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**UTILITY
PATENT APPLICATION
TRANSMITTAL**

(Only for nonprovisional applications under 37 CFR § 1.53(b))

Attorney Docket No.

210121.427C15

First Inventor or Application Identifier

Jiangchun Xu

Title

COMPOSITIONS AND METHODS FOR THE THERAPY
AND DIAGNOSIS OF PROSTATE CANCER

Express Mail Label No.

EL615230015US

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

1. General Authorization Form & Fee Transmittal
(Submit an original and a duplicate for fee processing)2. Specification [Total Pages] **201**
(preferred arrangement set forth below)

- Descriptive Title of the Invention
- Cross References to Related Applications
- Statement Regarding Fed sponsored R & D
- Reference to Microfiche Appendix
- Background of the Invention
- Brief Summary of the Invention
- Brief Description of the Drawings (if filed)
- Detailed Description
- Claim(s)
- Abstract of the Disclosure

3. Drawing(s) (35 USC 113) [Total Sheets] **16**4. Oath or Declaration [Total Pages] _____
 a. Newly executed (original or copy)
 b. Copy from a prior application (37 CFR 1.63(d))
(for continuation/divisional with Box 17 completed)
 i. **DELETION OF INVENTOR(S)**
 Signed statement attached deleting
 inventor(s) named in the prior application,
 see 37 CFR 1.63(d)(2) and 1.33(b)

5. Incorporation By Reference (useable if box 4b is checked) The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4b, is considered to be part of the disclosure of the accompanying application and is hereby incorporated by reference therein.

17. If a CONTINUING APPLICATION, check appropriate box and supply the requisite information below and in a preliminary amendment

 Continuation Divisional Continuation-In-Part (CIP) of prior Application No.: not assigned
Prior application information: Examiner not assigned Group / Art Unit not assigned
 Claims the benefit of Provisional Application No. _____
CORRESPONDENCE ADDRESS

Jane E. R. Potter
Seed Intellectual Property Law Group PLLC
 701 Fifth Avenue, Suite 6300
 Seattle, Washington 98104-7092
 Phone: (206) 622-4900 Fax: (206) 682-6031

Respectfully submitted,

TYPED or PRINTED NAME Jane E. R. Potter
 SIGNATURE Jane E. R. PotterREGISTRATION NO. 33,332
 Date June 13, 2000

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Jiangchun Xu, Bellevue, WA; Davin C. Dillon, Redmond, WA; Jennifer L. Mitcham, Redmond, WA; Susan L. Harlocker, Seattle, WA; Yuqiu Jiang, Kent, WA; Michael D. Kalos, Seattle, WA; Gary R. Fanger, Mill Creek, WA; Marc W. Retter, Carnation, WA; John A. Stolk, Bothell, WA; Craig H. Day, Seattle, WA; Thomas S. Vedvick, Bainbridge Island, WA; Darrick Carter, Seattle, WA; Samuel Li, Redmond, WA; Aijun Wang, Issaquah, WA; Yasir A. W. Skeiky, Seattle, WA; William Hepler, Seattle, WA; Robert A. Henderson, Seattle, WA

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Washington, DC 20231

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Assistant Commissioner for Patents:

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Respectfully submitted,

Seed Intellectual Property Law Group PLLC



Susan Johnson

Amber Straub/Jeanette West/Susan Johnson

Enclosures:

Postcard
Form PTO/SB/05
Specification, Claims, Abstract (201 pages)
16 Sheets of Drawings (Figures 1-12)
Sequence Listing (357 pages)
Declaration for Sequence Listing
Diskette for Sequence Listing

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COMPOSITIONS AND METHODS FOR THE THERAPY
AND DIAGNOSIS OF PROSTATE CANCER

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. Patent Application No. 5 09/_____, filed May 12, 2000, which is a continuation-in-part of U.S. Patent Application No. 09/568,100, filed May 9, 2000, which is a continuation-in-part of U.S. Patent Application No. 09/536,857, filed March 27, 2000, which is a continuation-in-part of U.S. Patent Application No. 09/483,672, filed January 14, 2000, which is a continuation-in-part of U.S. Patent Application No. 09/439,313, filed November 12, 1999, which is a continuation-in-part of U.S. Patent Application No. 09/352,616, filed July 13, 1999, which is a continuation-in-part of U.S. Patent Application No. 09/288,946, filed April 9, 1999, which is a continuation-in-part of U.S. Patent Application No. 09/232,149, filed January 15, 1999, which is a continuation-in-part of U.S. Patent Application No. 09/159,812, filed September 23, 1998, which is a continuation-in-part of U.S. Patent Application No. 15 09/115,453, filed July 14, 1998, which is a continuation-in-part of U.S. Patent Application No. 09/030,607, filed February 25, 1998, which is a continuation-in-part of U.S. Patent Application No. 09/020,956, filed February 9, 1998, which is a continuation-in-part of U.S. Patent Application No. 08/904,804, filed August 1, 1997, which is a continuation-in-part of U.S. Patent Application No. 08/806,099, filed February 25, 1997.

20 TECHNICAL FIELD OF THE INVENTION

The present invention relates generally to therapy and diagnosis of cancer, such as prostate cancer. The invention is more specifically related to polypeptides comprising at least a portion of a prostate-specific protein, and to polynucleotides encoding such polypeptides. Such polypeptides and polynucleotides may be used in compositions 25 for prevention and treatment of prostate cancer, and for the diagnosis and monitoring of such cancers.

BACKGROUND OF THE INVENTION

Cancer is a significant health problem throughout the world. Although Cancer is a significant health problem throughout the world. Although advances have been made in detection and therapy of cancer, no vaccine or other universally successful method 5 for prevention or treatment is currently available. Current therapies, which are generally based on a combination of chemotherapy or surgery and radiation, continue to prove inadequate in many patients.

Prostate cancer is the most common form of cancer among males, with an estimated incidence of 30% in men over the age of 50. Overwhelming clinical evidence 10 shows that human prostate cancer has the propensity to metastasize to bone, and the disease appears to progress inevitably from androgen dependent to androgen refractory status, leading to increased patient mortality. This prevalent disease is currently the second leading cause of cancer death among men in the U.S.

In spite of considerable research into therapies for the disease, prostate 15 cancer remains difficult to treat. Commonly, treatment is based on surgery and/or radiation therapy, but these methods are ineffective in a significant percentage of cases. Two previously identified prostate specific proteins - prostate specific antigen (PSA) and prostatic acid phosphatase (PAP) - have limited therapeutic and diagnostic potential. For example, PSA levels do not always correlate well with the presence of prostate cancer, 20 being positive in a percentage of non-prostate cancer cases, including benign prostatic hyperplasia (BPH). Furthermore, PSA measurements correlate with prostate volume, and do not indicate the level of metastasis.

In spite of considerable research into therapies for these and other cancers, prostate cancer remains difficult to diagnose and treat effectively. Accordingly, there is a 25 need in the art for improved methods for detecting and treating such cancers. The present invention fulfills these needs and further provides other related advantages.

SUMMARY OF THE INVENTION

Briefly stated, the present invention provides compositions and methods for the diagnosis and therapy of cancer, such as prostate cancer. In one aspect, the present invention provides polypeptides comprising at least a portion of a prostate-specific protein, or a variant thereof. Certain portions and other variants are immunogenic, such that the ability of the variant to react with antigen-specific antisera is not substantially diminished. Within certain embodiments, the polypeptide comprises a sequence that is encoded by a polynucleotide sequence selected from the group consisting of: (a) sequences recited in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 5 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 10 593-606, 618-705, 709-774, 777 and 789; (b) variants of a sequence recited in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777 and 789; and (c) complements of a sequence of (a) or (b). In 15 specific embodiments, the polypeptides of the present invention comprise at least a portion of a tumor protein that includes an amino acid sequence selected from the group consisting of sequences recited in SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380, 383, 477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568, 573-586, 588-590, 592, 706-708, 775, 776, 778 and 780, and variants thereof.

20 The present invention further provides polynucleotides that encode a polypeptide as described above, or a portion thereof (such as a portion encoding at least 15 amino acid residues of a prostate-specific protein), expression vectors comprising such polynucleotides and host cells transformed or transfected with such expression vectors.

25 Within other aspects, the present invention provides pharmaceutical compositions comprising a polypeptide or polynucleotide as described above and a physiologically acceptable carrier.

Within a related aspect of the present invention, immunogenic compositions, or vaccines for prophylactic or therapeutic use are provided. Such

compositions comprise a polypeptide or polynucleotide as described above and an immunostimulant.

The present invention further provides pharmaceutical compositions that comprise: (a) an antibody or antigen-binding fragment thereof that specifically binds to a prostate-specific protein; and (b) a physiologically acceptable carrier.

Within further aspects, the present invention provides pharmaceutical compositions comprising: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) a pharmaceutically acceptable carrier or excipient. Antigen presenting cells include dendritic cells, macrophages, monocytes, fibroblasts and B cells.

Within related aspects, immunogenic compositions, or vaccines, are provided that comprise: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) an immunostimulant.

The present invention further provides, in other aspects, fusion proteins that comprise at least one polypeptide as described above, as well as polynucleotides encoding such fusion proteins.

Within related aspects, pharmaceutical compositions comprising a fusion protein, or a polynucleotide encoding a fusion protein, in combination with a physiologically acceptable carrier are provided.

Compositions are further provided, within other aspects, that comprise a fusion protein, or a polynucleotide encoding a fusion protein, in combination with an immunostimulant.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient a composition as recited above. The patient may be afflicted with prostate cancer, in which case the methods provide treatment for the disease, or patient considered at risk for such a disease may be treated prophylactically.

The present invention further provides, within other aspects, methods for removing tumor cells from a biological sample, comprising contacting a biological sample with T cells that specifically react with a prostate-specific protein, wherein the step of

contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the protein from the sample.

Within related aspects, methods are provided for inhibiting the development of a cancer in a patient, comprising administering to a patient a biological sample treated as 5 described above.

Methods are further provided, within other aspects, for stimulating and/or expanding T cells specific for a prostate-specific protein, comprising contacting T cells with one or more of: (i) a polypeptide as described above; (ii) a polynucleotide encoding such a polypeptide; and/or (iii) an antigen presenting cell that expresses such a polypeptide; 10 under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells. Isolated T cell populations comprising T cells prepared as described above are also provided.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective 15 amount of a T cell population as described above.

The present invention further provides methods for inhibiting the development of a cancer in a patient, comprising the steps of: (a) incubating CD4⁺ and/or CD8⁺ T cells isolated from a patient with one or more of: (i) a polypeptide comprising at least an immunogenic portion of a prostate-specific protein; (ii) a polynucleotide encoding 20 such a polypeptide; and (iii) an antigen-presenting cell that expressed such a polypeptide; and (b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of a cancer in the patient. Proliferated cells may, but need not, be cloned prior to administration to the patient.

Within further aspects, the present invention provides methods for 25 determining the presence or absence of a cancer in a patient, comprising: (a) contacting a biological sample obtained from a patient with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; and (c) comparing the amount of polypeptide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient.

Within preferred embodiments, the binding agent is an antibody, more preferably a monoclonal antibody. The cancer may be prostate cancer.

The present invention also provides, within other aspects, methods for monitoring the progression of a cancer in a patient. Such methods comprise the steps of:

- 5 (a) contacting a biological sample obtained from a patient at a first point in time with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polypeptide detected in step (c) with the amount detected in step
- 10 (b) and therefrom monitoring the progression of the cancer in the patient.

The present invention further provides, within other aspects, methods for determining the presence or absence of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a prostate-specific protein; (b) detecting in the sample a level of a polynucleotide, preferably mRNA, that hybridizes to the oligonucleotide; and (c) comparing the level of polynucleotide that hybridizes to the oligonucleotide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within certain embodiments, the amount of mRNA is detected via polymerase chain reaction using, for example, at least one oligonucleotide primer that hybridizes to a polynucleotide encoding a polypeptide as recited above, or a complement of such a polynucleotide. Within other embodiments, the amount of mRNA is detected using a hybridization technique, employing an oligonucleotide probe that hybridizes to a polynucleotide that encodes a polypeptide as recited above, or a complement of such a polynucleotide.

25 In related aspects, methods are provided for monitoring the progression of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a prostate-specific protein; (b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; (c) repeating steps (a) and (b) using a biological sample

obtained from the patient at a subsequent point in time; and (d) comparing the amount of polynucleotide detected in step (c) with the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

Within further aspects, the present invention provides antibodies, such as 5 monoclonal antibodies, that bind to a polypeptide as described above, as well as diagnostic kits comprising such antibodies. Diagnostic kits comprising one or more oligonucleotide probes or primers as described above are also provided.

These and other aspects of the present invention will become apparent upon reference to the following detailed description and attached drawings. All references 10 disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

BRIEF DESCRIPTION OF THE DRAWINGS AND SEQUENCE IDENTIFIERS

Figure 1 illustrates the ability of T cells to kill fibroblasts expressing the representative prostate-specific polypeptide P502S, as compared to control fibroblasts. The 15 percentage lysis is shown as a series of effector:target ratios, as indicated.

Figures 2A and 2B illustrate the ability of T cells to recognize cells expressing the representative prostate-specific polypeptide P502S. In each case, the number of γ -interferon spots is shown for different numbers of responders. In Figure 2A, data is presented for fibroblasts pulsed with the P2S-12 peptide, as compared to fibroblasts 20 pulsed with a control E75 peptide. In Figure 2B, data is presented for fibroblasts expressing P502S, as compared to fibroblasts expressing HER-2/neu.

Figure 3 represents a peptide competition binding assay showing that the P1S#10 peptide, derived from P501S, binds HLA-A2. Peptide P1S#10 inhibits HLA-A2 restricted presentation of fluM58 peptide to CTL clone D150M58 in TNF release bioassay. 25 D150M58 CTL is specific for the HLA-A2 binding influenza matrix peptide fluM58.

Figure 4 illustrates the ability of T cell lines generated from P1S#10 immunized mice to specifically lyse P1S#10-pulsed Jurkat A2K_b targets and P501S-

transduced Jurkat A2Kb targets, as compared to EGFP-transduced Jurkat A2Kb. The percent lysis is shown as a series of effector to target ratios, as indicated.

Figure 5 illustrates the ability of a T cell clone to recognize and specifically lyse Jurkat A2Kb cells expressing the representative prostate-specific polypeptide P501S, 5 thereby demonstrating that the P1S#10 peptide may be a naturally processed epitope of the P501S polypeptide.

Figures 6A and 6B are graphs illustrating the specificity of a CD8⁺ cell line (3A-1) for a representative prostate-specific antigen (P501S). Figure 6A shows the results of a ⁵¹Cr release assay. The percent specific lysis is shown as a series of effector:target 10 ratios, as indicated. Figure 6B shows the production of interferon-gamma by 3A-1 cells stimulated with autologous B-LCL transduced with P501S, at varying effector:target ratios as indicated.

Figure 7 is a Western blot showing the expression of P501S in baculovirus.

Figure 8 illustrates the results of epitope mapping studies on P501S.

15 Figure 9 is a schematic representation of the P501S protein showing the location of transmembrane domains and predicted intracellular and extracellular domains.

Figure 10 is a genomic map showing the location of the prostate genes P775P, P704P, B305D, P712P and P774P within the Cat Eye Syndrome region of chromosome 22q11.2

20 Figure 11 shows the results of an ELISA assay to determine the specificity of rabbit polyclonal antisera raised against P501S.

Figures 12A(1), 12A(2), 12A(3), and B are the full-length cDNA (SEQ ID NO:591) and predicted amino acid (SEQ ID NO:592) sequences, respectively, for the clone P788P.

25 SEQ ID NO: 1 is the determined cDNA sequence for F1-13

SEQ ID NO: 2 is the determined 3' cDNA sequence for F1-12

SEQ ID NO: 3 is the determined 5' cDNA sequence for F1-12

SEQ ID NO: 4 is the determined 3' cDNA sequence for F1-16

SEQ ID NO: 5 is the determined 3' cDNA sequence for H1-1

SEQ ID NO: 6 is the determined 3' cDNA sequence for H1-9
SEQ ID NO: 7 is the determined 3' cDNA sequence for H1-4
SEQ ID NO: 8 is the determined 3' cDNA sequence for J1-17
SEQ ID NO: 9 is the determined 5' cDNA sequence for J1-17
5 SEQ ID NO: 10 is the determined 3' cDNA sequence for L1-12
SEQ ID NO: 11 is the determined 5' cDNA sequence for L1-12
SEQ ID NO: 12 is the determined 3' cDNA sequence for N1-1862
SEQ ID NO: 13 is the determined 5' cDNA sequence for N1-1862
SEQ ID NO: 14 is the determined 3' cDNA sequence for J1-13
10 SEQ ID NO: 15 is the determined 5' cDNA sequence for J1-13
SEQ ID NO: 16 is the determined 3' cDNA sequence for J1-19
SEQ ID NO: 17 is the determined 5' cDNA sequence for J1-19
SEQ ID NO: 18 is the determined 3' cDNA sequence for J1-25
SEQ ID NO: 19 is the determined 5' cDNA sequence for J1-25
15 SEQ ID NO: 20 is the determined 5' cDNA sequence for J1-24
SEQ ID NO: 21 is the determined 3' cDNA sequence for J1-24
SEQ ID NO: 22 is the determined 5' cDNA sequence for K1-58
SEQ ID NO: 23 is the determined 3' cDNA sequence for K1-58
SEQ ID NO: 24 is the determined 5' cDNA sequence for K1-63
20 SEQ ID NO: 25 is the determined 3' cDNA sequence for K1-63
SEQ ID NO: 26 is the determined 5' cDNA sequence for L1-4
SEQ ID NO: 27 is the determined 3' cDNA sequence for L1-4
SEQ ID NO: 28 is the determined 5' cDNA sequence for L1-14
SEQ ID NO: 29 is the determined 3' cDNA sequence for L1-14
25 SEQ ID NO: 30 is the determined 3' cDNA sequence for J1-12
SEQ ID NO: 31 is the determined 3' cDNA sequence for J1-16
SEQ ID NO: 32 is the determined 3' cDNA sequence for J1-21
SEQ ID NO: 33 is the determined 3' cDNA sequence for K1-48
SEQ ID NO: 34 is the determined 3' cDNA sequence for K1-55

SEQ ID NO: 35 is the determined 3' cDNA sequence for L1-2
SEQ ID NO: 36 is the determined 3' cDNA sequence for L1-6
SEQ ID NO: 37 is the determined 3' cDNA sequence for N1-1858
SEQ ID NO: 38 is the determined 3' cDNA sequence for N1-1860
5 SEQ ID NO: 39 is the determined 3' cDNA sequence for N1-1861
SEQ ID NO: 40 is the determined 3' cDNA sequence for N1-1864
SEQ ID NO: 41 is the determined cDNA sequence for P5
SEQ ID NO: 42 is the determined cDNA sequence for P8
SEQ ID NO: 43 is the determined cDNA sequence for P9
10 SEQ ID NO: 44 is the determined cDNA sequence for P18
SEQ ID NO: 45 is the determined cDNA sequence for P20
SEQ ID NO: 46 is the determined cDNA sequence for P29
SEQ ID NO: 47 is the determined cDNA sequence for P30
SEQ ID NO: 48 is the determined cDNA sequence for P34
15 SEQ ID NO: 49 is the determined cDNA sequence for P36
SEQ ID NO: 50 is the determined cDNA sequence for P38
SEQ ID NO: 51 is the determined cDNA sequence for P39
SEQ ID NO: 52 is the determined cDNA sequence for P42
SEQ ID NO: 53 is the determined cDNA sequence for P47
20 SEQ ID NO: 54 is the determined cDNA sequence for P49
SEQ ID NO: 55 is the determined cDNA sequence for P50
SEQ ID NO: 56 is the determined cDNA sequence for P53
SEQ ID NO: 57 is the determined cDNA sequence for P55
SEQ ID NO: 58 is the determined cDNA sequence for P60
25 SEQ ID NO: 59 is the determined cDNA sequence for P64
SEQ ID NO: 60 is the determined cDNA sequence for P65
SEQ ID NO: 61 is the determined cDNA sequence for P73
SEQ ID NO: 62 is the determined cDNA sequence for P75
SEQ ID NO: 63 is the determined cDNA sequence for P76

SEQ ID NO: 64 is the determined cDNA sequence for P79
SEQ ID NO: 65 is the determined cDNA sequence for P84
SEQ ID NO: 66 is the determined cDNA sequence for P68
SEQ ID NO: 67 is the determined cDNA sequence for P80 (also referred to
5 as P704P)
SEQ ID NO: 68 is the determined cDNA sequence for P82
SEQ ID NO: 69 is the determined cDNA sequence for U1-3064
SEQ ID NO: 70 is the determined cDNA sequence for U1-3065
SEQ ID NO: 71 is the determined cDNA sequence for V1-3692
10 SEQ ID NO: 72 is the determined cDNA sequence for 1A-3905
SEQ ID NO: 73 is the determined cDNA sequence for V1-3686
SEQ ID NO: 74 is the determined cDNA sequence for R1-2330
SEQ ID NO: 75 is the determined cDNA sequence for 1B-3976
SEQ ID NO: 76 is the determined cDNA sequence for V1-3679
15 SEQ ID NO: 77 is the determined cDNA sequence for 1G-4736
SEQ ID NO: 78 is the determined cDNA sequence for 1G-4738
SEQ ID NO: 79 is the determined cDNA sequence for 1G-4741
SEQ ID NO: 80 is the determined cDNA sequence for 1G-4744
SEQ ID NO: 81 is the determined cDNA sequence for 1G-4734
20 SEQ ID NO: 82 is the determined cDNA sequence for 1H-4774
SEQ ID NO: 83 is the determined cDNA sequence for 1H-4781
SEQ ID NO: 84 is the determined cDNA sequence for 1H-4785
SEQ ID NO: 85 is the determined cDNA sequence for 1H-4787
SEQ ID NO: 86 is the determined cDNA sequence for 1H-4796
25 SEQ ID NO: 87 is the determined cDNA sequence for 1I-4807
SEQ ID NO: 88 is the determined cDNA sequence for 1I-4810
SEQ ID NO: 89 is the determined cDNA sequence for 1I-4811
SEQ ID NO: 90 is the determined cDNA sequence for 1J-4876
SEQ ID NO: 91 is the determined cDNA sequence for 1K-4884

SEQ ID NO: 92 is the determined cDNA sequence for 1K-4896
SEQ ID NO: 93 is the determined cDNA sequence for 1G-4761
SEQ ID NO: 94 is the determined cDNA sequence for 1G-4762
SEQ ID NO: 95 is the determined cDNA sequence for 1H-4766
5 SEQ ID NO: 96 is the determined cDNA sequence for 1H-4770
SEQ ID NO: 97 is the determined cDNA sequence for 1H-4771
SEQ ID NO: 98 is the determined cDNA sequence for 1H-4772
SEQ ID NO: 99 is the determined cDNA sequence for 1D-4297
SEQ ID NO: 100 is the determined cDNA sequence for 1D-4309
10 SEQ ID NO: 101 is the determined cDNA sequence for 1D.1-4278
SEQ ID NO: 102 is the determined cDNA sequence for 1D-4288
SEQ ID NO: 103 is the determined cDNA sequence for 1D-4283
SEQ ID NO: 104 is the determined cDNA sequence for 1D-4304
SEQ ID NO: 105 is the determined cDNA sequence for 1D-4296
15 SEQ ID NO: 106 is the determined cDNA sequence for 1D-4280
SEQ ID NO: 107 is the determined full length cDNA sequence for F1-12
(also referred to as P504S)
SEQ ID NO: 108 is the predicted amino acid sequence for F1-12
SEQ ID NO: 109 is the determined full length cDNA sequence for J1-17
20 SEQ ID NO: 110 is the determined full length cDNA sequence for L1-12
(also referred to as P501S)
SEQ ID NO: 111 is the determined full length cDNA sequence for N1-1862
(also referred to as P503S)
SEQ ID NO: 112 is the predicted amino acid sequence for J1-17
25 SEQ ID NO: 113 is the predicted amino acid sequence for L1-12 (also
referred to as P501S)
SEQ ID NO: 114 is the predicted amino acid sequence for N1-1862 (also
referred to as P503S)
SEQ ID NO: 115 is the determined cDNA sequence for P89

SEQ ID NO: 116 is the determined cDNA sequence for P90
SEQ ID NO: 117 is the determined cDNA sequence for P92
SEQ ID NO: 118 is the determined cDNA sequence for P95
SEQ ID NO: 119 is the determined cDNA sequence for P98
5 SEQ ID NO: 120 is the determined cDNA sequence for P102
SEQ ID NO: 121 is the determined cDNA sequence for P110
SEQ ID NO: 122 is the determined cDNA sequence for P111
SEQ ID NO: 123 is the determined cDNA sequence for P114
SEQ ID NO: 124 is the determined cDNA sequence for P115
10 SEQ ID NO: 125 is the determined cDNA sequence for P116
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SEQ ID NO: 131 is the determined cDNA sequence for P143
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SEQ ID NO: 133 is the determined cDNA sequence for P156
SEQ ID NO: 134 is the determined cDNA sequence for P157
20 SEQ ID NO: 135 is the determined cDNA sequence for P166
SEQ ID NO: 136 is the determined cDNA sequence for P176
SEQ ID NO: 137 is the determined cDNA sequence for P178
SEQ ID NO: 138 is the determined cDNA sequence for P179
SEQ ID NO: 139 is the determined cDNA sequence for P185
25 SEQ ID NO: 140 is the determined cDNA sequence for P192
SEQ ID NO: 141 is the determined cDNA sequence for P201
SEQ ID NO: 142 is the determined cDNA sequence for P204
SEQ ID NO: 143 is the determined cDNA sequence for P208
SEQ ID NO: 144 is the determined cDNA sequence for P211

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SEQ ID NO: 160 is the determined cDNA sequence for P278
SEQ ID NO: 161 is the determined cDNA sequence for P105
SEQ ID NO: 162 is the determined cDNA sequence for P107
SEQ ID NO: 163 is the determined cDNA sequence for P137
20 SEQ ID NO: 164 is the determined cDNA sequence for P194
SEQ ID NO: 165 is the determined cDNA sequence for P195
SEQ ID NO: 166 is the determined cDNA sequence for P196
SEQ ID NO: 167 is the determined cDNA sequence for P220
SEQ ID NO: 168 is the determined cDNA sequence for P234
25 SEQ ID NO: 169 is the determined cDNA sequence for P235
SEQ ID NO: 170 is the determined cDNA sequence for P243
SEQ ID NO: 171 is the determined cDNA sequence for P703P-DE1
SEQ ID NO: 172 is the predicted amino acid sequence for P703P-DE1
SEQ ID NO: 173 is the determined cDNA sequence for P703P-DE2

SEQ ID NO: 174 is the determined cDNA sequence for P703P-DE6
SEQ ID NO: 175 is the determined cDNA sequence for P703P-DE13
SEQ ID NO: 176 is the predicted amino acid sequence for P703P-DE13
SEQ ID NO: 177 is the determined cDNA sequence for P703P-DE14
5 SEQ ID NO: 178 is the predicted amino acid sequence for P703P-DE14
SEQ ID NO: 179 is the determined extended cDNA sequence for 1G-4736
SEQ ID NO: 180 is the determined extended cDNA sequence for 1G-4738
SEQ ID NO: 181 is the determined extended cDNA sequence for 1G-4741
SEQ ID NO: 182 is the determined extended cDNA sequence for 1G-4744
10 SEQ ID NO: 183 is the determined extended cDNA sequence for 1H-4774
SEQ ID NO: 184 is the determined extended cDNA sequence for 1H-4781
SEQ ID NO: 185 is the determined extended cDNA sequence for 1H-4785
SEQ ID NO: 186 is the determined extended cDNA sequence for 1H-4787
SEQ ID NO: 187 is the determined extended cDNA sequence for 1H-4796
15 SEQ ID NO: 188 is the determined extended cDNA sequence for 1I-4807
SEQ ID NO: 189 is the determined 3' cDNA sequence for 1I-4810
SEQ ID NO: 190 is the determined 3' cDNA sequence for 1I-4811
SEQ ID NO: 191 is the determined extended cDNA sequence for 1J-4876
SEQ ID NO: 192 is the determined extended cDNA sequence for 1K-4884
20 SEQ ID NO: 193 is the determined extended cDNA sequence for 1K-4896
SEQ ID NO: 194 is the determined extended cDNA sequence for 1G-4761
SEQ ID NO: 195 is the determined extended cDNA sequence for 1G-4762
SEQ ID NO: 196 is the determined extended cDNA sequence for 1H-4766
SEQ ID NO: 197 is the determined 3' cDNA sequence for 1H-4770
25 SEQ ID NO: 198 is the determined 3' cDNA sequence for 1H-4771
SEQ ID NO: 199 is the determined extended cDNA sequence for 1H-4772
SEQ ID NO: 200 is the determined extended cDNA sequence for 1D-4309
SEQ ID NO: 201 is the determined extended cDNA sequence for 1D.1-4278
SEQ ID NO: 202 is the determined extended cDNA sequence for 1D-4288

SEQ ID NO: 203 is the determined extended cDNA sequence for 1D-4283
SEQ ID NO: 204 is the determined extended cDNA sequence for 1D-4304
SEQ ID NO: 205 is the determined extended cDNA sequence for 1D-4296
SEQ ID NO: 206 is the determined extended cDNA sequence for 1D-4280
5 SEQ ID NO: 207 is the determined cDNA sequence for 10-d8fwd
SEQ ID NO: 208 is the determined cDNA sequence for 10-H10con
SEQ ID NO: 209 is the determined cDNA sequence for 11-C8rev
SEQ ID NO: 210 is the determined cDNA sequence for 7.g6fwd
SEQ ID NO: 211 is the determined cDNA sequence for 7.g6rev
10 SEQ ID NO: 212 is the determined cDNA sequence for 8-b5fwd
SEQ ID NO: 213 is the determined cDNA sequence for 8-b5rev
SEQ ID NO: 214 is the determined cDNA sequence for 8-b6fwd
SEQ ID NO: 215 is the determined cDNA sequence for 8-b6 rev
SEQ ID NO: 216 is the determined cDNA sequence for 8-d4fwd
15 SEQ ID NO: 217 is the determined cDNA sequence for 8-d9rev
SEQ ID NO: 218 is the determined cDNA sequence for 8-g3fwd
SEQ ID NO: 219 is the determined cDNA sequence for 8-g3rev
SEQ ID NO: 220 is the determined cDNA sequence for 8-h11rev
SEQ ID NO: 221 is the determined cDNA sequence for g-f12fwd
20 SEQ ID NO: 222 is the determined cDNA sequence for g-f3rev
SEQ ID NO: 223 is the determined cDNA sequence for P509S
SEQ ID NO: 224 is the determined cDNA sequence for P510S
SEQ ID NO: 225 is the determined cDNA sequence for P703DE5
SEQ ID NO: 226 is the determined cDNA sequence for 9-A11
25 SEQ ID NO: 227 is the determined cDNA sequence for 8-C6
SEQ ID NO: 228 is the determined cDNA sequence for 8-H7
SEQ ID NO: 229 is the determined cDNA sequence for JPTPN13
SEQ ID NO: 230 is the determined cDNA sequence for JPTPN14
SEQ ID NO: 231 is the determined cDNA sequence for JPTPN23

SEQ ID NO: 232 is the determined cDNA sequence for JPTPN24
SEQ ID NO: 233 is the determined cDNA sequence for JPTPN25
SEQ ID NO: 234 is the determined cDNA sequence for JPTPN30
SEQ ID NO: 235 is the determined cDNA sequence for JPTPN34
5 SEQ ID NO: 236 is the determined cDNA sequence for PTPN35
SEQ ID NO: 237 is the determined cDNA sequence for JPTPN36
SEQ ID NO: 238 is the determined cDNA sequence for JPTPN38
SEQ ID NO: 239 is the determined cDNA sequence for JPTPN39
SEQ ID NO: 240 is the determined cDNA sequence for JPTPN40
10 SEQ ID NO: 241 is the determined cDNA sequence for JPTPN41
SEQ ID NO: 242 is the determined cDNA sequence for JPTPN42
SEQ ID NO: 243 is the determined cDNA sequence for JPTPN45
SEQ ID NO: 244 is the determined cDNA sequence for JPTPN46
SEQ ID NO: 245 is the determined cDNA sequence for JPTPN51
15 SEQ ID NO: 246 is the determined cDNA sequence for JPTPN56
SEQ ID NO: 247 is the determined cDNA sequence for PTPN64
SEQ ID NO: 248 is the determined cDNA sequence for JPTPN65
SEQ ID NO: 249 is the determined cDNA sequence for JPTPN67
SEQ ID NO: 250 is the determined cDNA sequence for JPTPN76
20 SEQ ID NO: 251 is the determined cDNA sequence for JPTPN84
SEQ ID NO: 252 is the determined cDNA sequence for JPTPN85
SEQ ID NO: 253 is the determined cDNA sequence for JPTPN86
SEQ ID NO: 254 is the determined cDNA sequence for JPTPN87
SEQ ID NO: 255 is the determined cDNA sequence for JPTPN88
25 SEQ ID NO: 256 is the determined cDNA sequence for JP1F1
SEQ ID NO: 257 is the determined cDNA sequence for JP1F2
SEQ ID NO: 258 is the determined cDNA sequence for JP1C2
SEQ ID NO: 259 is the determined cDNA sequence for JP1B1
SEQ ID NO: 260 is the determined cDNA sequence for JP1B2

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SEQ ID NO: 261 is the determined cDNA sequence for JP1D3
SEQ ID NO: 262 is the determined cDNA sequence for JP1A4
SEQ ID NO: 263 is the determined cDNA sequence for JP1F5
SEQ ID NO: 264 is the determined cDNA sequence for JP1E6
5 SEQ ID NO: 265 is the determined cDNA sequence for JP1D6
SEQ ID NO: 266 is the determined cDNA sequence for JP1B5
SEQ ID NO: 267 is the determined cDNA sequence for JP1A6
SEQ ID NO: 268 is the determined cDNA sequence for JP1E8
SEQ ID NO: 269 is the determined cDNA sequence for JP1D7
10 SEQ ID NO: 270 is the determined cDNA sequence for JP1D9
SEQ ID NO: 271 is the determined cDNA sequence for JP1C10
SEQ ID NO: 272 is the determined cDNA sequence for JP1A9
SEQ ID NO: 273 is the determined cDNA sequence for JP1F12
SEQ ID NO: 274 is the determined cDNA sequence for JP1E12
15 SEQ ID NO: 275 is the determined cDNA sequence for JP1D11
SEQ ID NO: 276 is the determined cDNA sequence for JP1C11
SEQ ID NO: 277 is the determined cDNA sequence for JP1C12
SEQ ID NO: 278 is the determined cDNA sequence for JP1B12
SEQ ID NO: 279 is the determined cDNA sequence for JP1A12
20 SEQ ID NO: 280 is the determined cDNA sequence for JP8G2
SEQ ID NO: 281 is the determined cDNA sequence for JP8H1
SEQ ID NO: 282 is the determined cDNA sequence for JP8H2
SEQ ID NO: 283 is the determined cDNA sequence for JP8A3
SEQ ID NO: 284 is the determined cDNA sequence for JP8A4
25 SEQ ID NO: 285 is the determined cDNA sequence for JP8C3
SEQ ID NO: 286 is the determined cDNA sequence for JP8G4
SEQ ID NO: 287 is the determined cDNA sequence for JP8B6
SEQ ID NO: 288 is the determined cDNA sequence for JP8D6
SEQ ID NO: 289 is the determined cDNA sequence for JP8F5

SEQ ID NO: 290 is the determined cDNA sequence for JP8A8
SEQ ID NO: 291 is the determined cDNA sequence for JP8C7
SEQ ID NO: 292 is the determined cDNA sequence for JP8D7
SEQ ID NO: 293 is the determined cDNA sequence for P8D8
5 SEQ ID NO: 294 is the determined cDNA sequence for JP8E7
SEQ ID NO: 295 is the determined cDNA sequence for JP8F8
SEQ ID NO: 296 is the determined cDNA sequence for JP8G8
SEQ ID NO: 297 is the determined cDNA sequence for JP8B10
SEQ ID NO: 298 is the determined cDNA sequence for JP8C10
10 SEQ ID NO: 299 is the determined cDNA sequence for JP8E9
SEQ ID NO: 300 is the determined cDNA sequence for JP8E10
SEQ ID NO: 301 is the determined cDNA sequence for JP8F9
SEQ ID NO: 302 is the determined cDNA sequence for JP8H9
SEQ ID NO: 303 is the determined cDNA sequence for JP8C12
15 SEQ ID NO: 304 is the determined cDNA sequence for JP8E11
SEQ ID NO: 305 is the determined cDNA sequence for JP8E12
SEQ ID NO: 306 is the amino acid sequence for the peptide PS2#12
SEQ ID NO: 307 is the determined cDNA sequence for P711P
SEQ ID NO: 308 is the determined cDNA sequence for P712P
20 SEQ ID NO: 309 is the determined cDNA sequence for CLONE23
SEQ ID NO: 310 is the determined cDNA sequence for P774P
SEQ ID NO: 311 is the determined cDNA sequence for P775P
SEQ ID NO: 312 is the determined cDNA sequence for P715P
SEQ ID NO: 313 is the determined cDNA sequence for P710P
25 SEQ ID NO: 314 is the determined cDNA sequence for P767P
SEQ ID NO: 315 is the determined cDNA sequence for P768P
SEQ ID NO: 316-325 are the determined cDNA sequences of previously
isolated genes
SEQ ID NO: 326 is the determined cDNA sequence for P703PDE5

SEQ ID NO: 327 is the predicted amino acid sequence for P703PDE5
SEQ ID NO: 328 is the determined cDNA sequence for P703P6.26
SEQ ID NO: 329 is the predicted amino acid sequence for P703P6.26
SEQ ID NO: 330 is the determined cDNA sequence for P703PX-23
5 SEQ ID NO: 331 is the predicted amino acid sequence for P703PX-23
SEQ ID NO: 332 is the determined full length cDNA sequence for P509S
SEQ ID NO: 333 is the determined extended cDNA sequence for P707P
(also referred to as 11-C9)
SEQ ID NO: 334 is the determined cDNA sequence for P714P
10 SEQ ID NO: 335 is the determined cDNA sequence for P705P (also referred to as 9-F3)
SEQ ID NO: 336 is the predicted amino acid sequence for P705P
SEQ ID NO: 337 is the amino acid sequence of the peptide P1S#10
SEQ ID NO: 338 is the amino acid sequence of the peptide p5
15 SEQ ID NO: 339 is the predicted amino acid sequence of P509S
SEQ ID NO: 340 is the determined cDNA sequence for P778P
SEQ ID NO: 341 is the determined cDNA sequence for P786P
SEQ ID NO: 342 is the determined cDNA sequence for P789P
SEQ ID NO: 343 is the determined cDNA sequence for a clone showing
20 homology to Homo sapiens MM46 mRNA
SEQ ID NO: 344 is the determined cDNA sequence for a clone showing homology to Homo sapiens TNF-alpha stimulated ABC protein (ABC50) mRNA
SEQ ID NO: 345 is the determined cDNA sequence for a clone showing homology to Homo sapiens mRNA for E-cadherin
25 SEQ ID NO: 346 is the determined cDNA sequence for a clone showing homology to Human nuclear-encoded mitochondrial serine hydroxymethyltransferase (SHMT)
SEQ ID NO: 347 is the determined cDNA sequence for a clone showing homology to Homo sapiens natural resistance-associated macrophage protein2 (NRAMP2)

SEQ ID NO: 348 is the determined cDNA sequence for a clone showing homology to Homo sapiens phosphoglucomutase-related protein (PGMRP)

SEQ ID NO: 349 is the determined cDNA sequence for a clone showing homology to Human mRNA for proteosome subunit p40

5 SEQ ID NO: 350 is the determined cDNA sequence for P777P

SEQ ID NO: 351 is the determined cDNA sequence for P779P

SEQ ID NO: 352 is the determined cDNA sequence for P790P

SEQ ID NO: 353 is the determined cDNA sequence for P784P

SEQ ID NO: 354 is the determined cDNA sequence for P776P

10 SEQ ID NO: 355 is the determined cDNA sequence for P780P

SEQ ID NO: 356 is the determined cDNA sequence for P544S

SEQ ID NO: 357 is the determined cDNA sequence for P745S

SEQ ID NO: 358 is the determined cDNA sequence for P782P

SEQ ID NO: 359 is the determined cDNA sequence for P783P

15 SEQ ID NO: 360 is the determined cDNA sequence for unknown 17984

SEQ ID NO: 361 is the determined cDNA sequence for P787P

SEQ ID NO: 362 is the determined cDNA sequence for P788P

SEQ ID NO: 363 is the determined cDNA sequence for unknown 17994

SEQ ID NO: 364 is the determined cDNA sequence for P781P

20 SEQ ID NO: 365 is the determined cDNA sequence for P785P

SEQ ID NO: 366-375 are the determined cDNA sequences for splice variants of B305D.

SEQ ID NO: 376 is the predicted amino acid sequence encoded by the sequence of SEQ ID NO: 366.

25 SEQ ID NO: 377 is the predicted amino acid sequence encoded by the sequence of SEQ ID NO: 372.

SEQ ID NO: 378 is the predicted amino acid sequence encoded by the sequence of SEQ ID NO: 373.

SEQ ID NO: 379 is the predicted amino acid sequence encoded by the sequence of SEQ ID NO: 374.

SEQ ID NO: 380 is the predicted amino acid sequence encoded by the sequence of SEQ ID NO: 375.

5 SEQ ID NO: 381 is the determined cDNA sequence for B716P.

SEQ ID NO: 382 is the determined full-length cDNA sequence for P711P.

SEQ ID NO: 383 is the predicted amino acid sequence for P711P.

SEQ ID NO: 384 is the cDNA sequence for P1000C.

SEQ ID NO: 385 is the cDNA sequence for CGI-82.

10 SEQ ID NO:386 is the cDNA sequence for 23320.

SEQ ID NO:387 is the cDNA sequence for CGI-69.

SEQ ID NO:388 is the cDNA sequence for L-iditol-2-dehydrogenase.

SEQ ID NO:389 is the cDNA sequence for 23379.

SEQ ID NO:390 is the cDNA sequence for 23381.

15 SEQ ID NO:391 is the cDNA sequence for KIAA0122.

SEQ ID NO:392 is the cDNA sequence for 23399.

SEQ ID NO:393 is the cDNA sequence for a previously identified gene.

SEQ ID NO:394 is the cDNA sequence for HCLBP.

SEQ ID NO:395 is the cDNA sequence for transglutaminase.

20 SEQ ID NO:396 is the cDNA sequence for a previously identified gene.

SEQ ID NO:397 is the cDNA sequence for PAP.

SEQ ID NO:398 is the cDNA sequence for Ets transcription factor PDEF.

SEQ ID NO:399 is the cDNA sequence for hTGR.

SEQ ID NO:400 is the cDNA sequence for KIAA0295.

25 SEQ ID NO:401 is the cDNA sequence for 22545.

SEQ ID NO:402 is the cDNA sequence for 22547.

SEQ ID NO:403 is the cDNA sequence for 22548.

SEQ ID NO:404 is the cDNA sequence for 22550.

SEQ ID NO:405 is the cDNA sequence for 22551.

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SEQ ID NO:406 is the cDNA sequence for 22552.
SEQ ID NO:407 is the cDNA sequence for 22553 (also known as P1020C).
SEQ ID NO:408 is the cDNA sequence for 22558.
SEQ ID NO:409 is the cDNA sequence for 22562.
5 SEQ ID NO:410 is the cDNA sequence for 22565.
SEQ ID NO:411 is the cDNA sequence for 22567.
SEQ ID NO:412 is the cDNA sequence for 22568.
SEQ ID NO:413 is the cDNA sequence for 22570.
SEQ ID NO:414 is the cDNA sequence for 22571.
10 SEQ ID NO:415 is the cDNA sequence for 22572.
SEQ ID NO:416 is the cDNA sequence for 22573.
SEQ ID NO:417 is the cDNA sequence for 22573.
SEQ ID NO:418 is the cDNA sequence for 22575.
SEQ ID NO:419 is the cDNA sequence for 22580.
15 SEQ ID NO:420 is the cDNA sequence for 22581.
SEQ ID NO:421 is the cDNA sequence for 22582.
SEQ ID NO:422 is the cDNA sequence for 22583.
SEQ ID NO:423 is the cDNA sequence for 22584.
SEQ ID NO:424 is the cDNA sequence for 22585.
20 SEQ ID NO:425 is the cDNA sequence for 22586.
SEQ ID NO:426 is the cDNA sequence for 22587.
SEQ ID NO:427 is the cDNA sequence for 22588.
SEQ ID NO:428 is the cDNA sequence for 22589.
SEQ ID NO:429 is the cDNA sequence for 22590.
25 SEQ ID NO:430 is the cDNA sequence for 22591.
SEQ ID NO:431 is the cDNA sequence for 22592.
SEQ ID NO:432 is the cDNA sequence for 22593.
SEQ ID NO:433 is the cDNA sequence for 22594.
SEQ ID NO:434 is the cDNA sequence for 22595.

SEQ ID NO:435 is the cDNA sequence for 22596.
SEQ ID NO:436 is the cDNA sequence for 22847.
SEQ ID NO:437 is the cDNA sequence for 22848.
SEQ ID NO:438 is the cDNA sequence for 22849.
5 SEQ ID NO:439 is the cDNA sequence for 22851.
SEQ ID NO:440 is the cDNA sequence for 22852.
SEQ ID NO:441 is the cDNA sequence for 22853.
SEQ ID NO:442 is the cDNA sequence for 22854.
SEQ ID NO:443 is the cDNA sequence for 22855.
10 SEQ ID NO:444 is the cDNA sequence for 22856.
SEQ ID NO:445 is the cDNA sequence for 22857.
SEQ ID NO:446 is the cDNA sequence for 23601.
SEQ ID NO:447 is the cDNA sequence for 23602.
SEQ ID NO:448 is the cDNA sequence for 23605.
15 SEQ ID NO:449 is the cDNA sequence for 23606.
SEQ ID NO:450 is the cDNA sequence for 23612.
SEQ ID NO:451 is the cDNA sequence for 23614.
SEQ ID NO:452 is the cDNA sequence for 23618.
SEQ ID NO:453 is the cDNA sequence for 23622.
20 SEQ ID NO:454 is the cDNA sequence for folate hydrolase.
SEQ ID NO:455 is the cDNA sequence for LIM protein.
SEQ ID NO:456 is the cDNA sequence for a known gene.
SEQ ID NO:457 is the cDNA sequence for a known gene.
SEQ ID NO:458 is the cDNA sequence for a previously identified gene.
25 SEQ ID NO:459 is the cDNA sequence for 23045.
SEQ ID NO:460 is the cDNA sequence for 23032.
SEQ ID NO:461 is the cDNA sequence for 23054.
SEQ ID NO:462-467 are cDNA sequences for known genes.
SEQ ID NO:468-471 are cDNA sequences for P710P.

SEQ ID NO:472 is a cDNA sequence for P1001C.

SEQ ID NO: 473 is the determined cDNA sequence for a first splice variant of P775P (referred to as 27505).

SEQ ID NO: 474 is the determined cDNA sequence for a second splice
5 variant of P775P (referred to as 19947).

SEQ ID NO: 475 is the determined cDNA sequence for a third splice variant of P775P (referred to as 19941).

SEQ ID NO: 476 is the determined cDNA sequence for a fourth splice variant of P775P (referred to as 19937).

10 SEQ ID NO: 477 is a first predicted amino acid sequence encoded by the sequence of SEQ ID NO: 474.

SEQ ID NO: 478 is a second predicted amino acid sequence encoded by the sequence of SEQ ID NO: 474.

15 SEQ ID NO: 479 is the predicted amino acid sequence encoded by the sequence of SEQ ID NO: 475.

SEQ ID NO: 480 is a first predicted amino acid sequence encoded by the sequence of SEQ ID NO: 473.

SEQ ID NO: 481 is a second predicted amino acid sequence encoded by the sequence of SEQ ID NO: 473.

20 SEQ ID NO: 482 is a third predicted amino acid sequence encoded by the sequence of SEQ ID NO: 473.

SEQ ID NO: 483 is a fourth predicted amino acid sequence encoded by the sequence of SEQ ID NO: 473.

SEQ ID NO: 484 is the first 30 amino acids of the *M. tuberculosis* antigen
25 Ra12.

SEQ ID NO: 485 is the PCR primer AW025.

SEQ ID NO: 486 is the PCR primer AW003.

SEQ ID NO: 487 is the PCR primer AW027.

SEQ ID NO: 488 is the PCR primer AW026.

SEQ ID NO: 489-501 are peptides employed in epitope mapping studies.

SEQ ID NO: 502 is the determined cDNA sequence of the complementarity determining region for the anti-P503S monoclonal antibody 20D4.

SEQ ID NO: 503 is the determined cDNA sequence of the complementarity 5 determining region for the anti-P503S monoclonal antibody JA1.

SEQ ID NO: 504 & 505 are peptides employed in epitope mapping studies.

SEQ ID NO: 506 is the determined cDNA sequence of the complementarity determining region for the anti-P703P monoclonal antibody 8H2.

SEQ ID NO: 507 is the determined cDNA sequence of the complementarity 10 determining region for the anti-P703P monoclonal antibody 7H8.

SEQ ID NO: 508 is the determined cDNA sequence of the complementarity determining region for the anti-P703P monoclonal antibody 2D4.

SEQ ID NO: 509-522 are peptides employed in epitope mapping studies.

SEQ ID NO: 523 is a mature form of P703P used to raise antibodies against 15 P703P.

SEQ ID NO: 524 is the putative full-length cDNA sequence of P703P.

SEQ ID NO: 525 is the predicted amino acid sequence encoded by SEQ ID NO: 524.

SEQ ID NO: 526 is the full-length cDNA sequence for P790P.

20 SEQ ID NO: 527 is the predicted amino acid sequence for P790P.

SEQ ID NO: 528 & 529 are PCR primers.

SEQ ID NO: 530 is the cDNA sequence of a splice variant of SEQ ID NO: 366.

SEQ ID NO: 531 is the cDNA sequence of the open reading frame of SEQ 25 ID NO: 530.

SEQ ID NO: 532 is the predicted amino acid encoded by the sequence of SEQ ID NO: 531.

SEQ ID NO: 533 is the DNA sequence of a putative ORF of P775P.

SEQ ID NO: 534 is the predicted amino acid sequence encoded by SEQ ID NO: 533.

SEQ ID NO: 535 is a first full-length cDNA sequence for P510S.

SEQ ID NO: 536 is a second full-length cDNA sequence for P510S.

5 SEQ ID NO: 537 is the predicted amino acid sequence encoded by SEQ ID NO: 535.

SEQ ID NO: 538 is the predicted amino acid sequence encoded by SEQ ID NO: 536.

SEQ ID NO: 539 is the peptide P501S-370.

10 SEQ ID NO: 540 is the peptide P501S-376.

SEQ ID NO: 541-551 are epitopes of P501S.

SEQ ID NO: 552 is an extended cDNA sequence for P712P.

SEQ ID NO: 553-568 are the amino acid sequences encoded by predicted open reading frames within SEQ ID NO: 552.

15 SEQ ID NO: 569 is an extended cDNA sequence for P776P.

SEQ ID NO: 570 is the determined cDNA sequence for a splice variant of P776P referred to as contig 6.

SEQ ID NO: 571 is the determined cDNA sequence for a splice variant of P776P referred to as contig 7.

20 SEQ ID NO: 572 is the determined cDNA sequence for a splice variant of P776P referred to as contig 14.

SEQ ID NO: 573 is the amino acid sequence encoded by a first predicted ORF of SEQ ID NO: 570.

25 SEQ ID NO: 574 is the amino acid sequence encoded by a second predicted ORF of SEQ ID NO: 570.

SEQ ID NO: 575 is the amino acid sequence encoded by a predicted ORF of SEQ ID NO: 571.

SEQ ID NO: 576-586 are amino acid sequences encoded by predicted ORFs of SEQ ID NO: 569.

SEQ ID NO: 587 is a DNA consensus sequence of the sequences of P767P and P777P.

SEQ ID NO: 588-590 are amino acid sequences encoded by predicted ORFs of SEQ ID NO: 587.

5 SEQ ID NO: 591 is an extended cDNA sequence for P1020C.

SEQ ID NO: 592 is the predicted amino acid sequence encoded by the sequence of SEQ ID NO: P1020C.

SEQ ID NO: 593 is a splice variant of P775P referred to as 50748.

10 SEQ ID NO: 594 is a splice variant of P775P referred to as 50717. SEQ ID NO: 595 is a splice variant of P775P referred to as 45985.

SEQ ID NO: 596 is a splice variant of P775P referred to as 38769.

SEQ ID NO: 597 is a splice variant of P775P referred to as 37922.

SEQ ID NO: 598 is a splice variant of P510S referred to as 49274.

SEQ ID NO: 599 is a splice variant of P510S referred to as 39487.

15 SEQ ID NO: 600 is a splice variant of P504S referred to as 5167.16.

SEQ ID NO: 601 is a splice variant of P504S referred to as 5167.1.

SEQ ID NO: 602 is a splice variant of P504S referred to as 5163.46.

SEQ ID NO: 603 is a splice variant of P504S referred to as 5163.42.

SEQ ID NO: 604 is a splice variant of P504S referred to as 5163.34.

20 SEQ ID NO: 605 is a splice variant of P504S referred to as 5163.17.

SEQ ID NO: 606 is a splice variant of P501S referred to as 10640.

SEQ ID NO: 607-615 are the sequences of PCR primers.

SEQ ID NO: 616 is the determined cDNA sequence of a fusion of P703P and PSA.

25 SEQ ID NO: 617 is the amino acid sequence of the fusion of P703P and PSA.

SEQ ID NO: 618-689 are determined cDNA sequences of prostate-specific clones.

SEQ ID NO: 690 is the cDNA sequence of the gene DD3.

SEQ ID NO: 691-697 are determined cDNA sequences of prostate-specific clones.

SEQ ID NO: 698 is an extended cDNA sequence for P714P.

SEQ ID NO: 699-701 are the cDNA sequences for splice variants of P704P.

5 SEQ ID NO: 702 is the cDNA sequence of a spliced variant of P553S referred to as P553S-14.

SEQ ID NO: 703 is the cDNA sequence of a spliced variant of P553S referred to as P553S-12.

10 SEQ ID NO: 704 is the cDNA sequence of a spliced variant of P553S referred to as P553S-10.

SEQ ID NO: 705 is the cDNA sequence of a spliced variant of P553S referred to as P553S-6.

SEQ ID NO: 706 is the amino acid sequence encoded by SEQ ID NO: 705.

15 SEQ ID NO: 707 is the amino acid sequence encoded by SEQ ID NO: 702 SEQ ID NO: 708 is a second amino acid sequence encoded by SEQ ID NO: 702.

SEQ ID NO: 709-772 are determined cDNA sequences of prostate-specific clones.

SEQ ID NO: 773 is a first full-length cDNA sequence for prostate-specific transglutaminase gene (also referred to herein as P558S).

20 SEQ ID NO: 774 is a second full-length cDNA sequence for prostate-specific transglutaminase gene.

SEQ ID NO: 775 is the amino acid sequence encoded by the sequence of SEQ ID NO: 773.

25 SEQ ID NO: 776 is the amino acid sequence encoded by the sequence of SEQ ID NO: 774.

SEQ ID NO: 777 is the full-length cDNA sequence for P788P.

SEQ ID NO: 778 is the amino acid sequence encoded by SEQ ID NO: 777.

SEQ ID NO: 779 is the determined cDNA sequence for a polymorphic variant of P788P.

SEQ ID NO: 780 is the amino acid sequence encoded by SEQ ID NO: 779.

SEQ ID NO: 781 is the amino acid sequence of peptide 4 from P703P.

SEQ ID NO: 782 is the cDNA sequence that encodes peptide 4 from P703P.

SEQ ID NO: 783-798 are the cDNA sequence encoding epitopes of P703P.

5 SEQ ID NO: 799-814 are the amino acid sequences of epitopes of P703P.

DETAILED DESCRIPTION OF THE INVENTION

As noted above, the present invention is generally directed to compositions and methods for using the compositions, for example in the therapy and diagnosis of cancer, such as prostate cancer. Certain illustrative compositions described herein include
10 prostate-specific polypeptides, polynucleotides encoding such polypeptides, binding agents such as antibodies, antigen presenting cells (APCs) and/or immune system cells (*e.g.*, T cells). A "prostate-specific protein," as the term is used herein, refers generally to a protein that is expressed in prostate cells at a level that is at least two fold, and preferably at least five fold, greater than the level of expression in other normal tissues, as determined using a
15 representative assay provided herein. Certain prostate-specific proteins are tumor proteins that react detectably (within an immunoassay, such as an ELISA or Western blot) with antisera of a patient afflicted with prostate cancer.

Therefore, in accordance with the above, and as described further below, the present invention provides illustrative polynucleotide compositions having sequences set
20 forth in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777 and 789, illustrative polypeptide compositions having amino acid sequences set forth in SEQ ID NO: 112-114, 172, 176, 178, 327, 329,
25 331, 336, 339, 376-380, 383, 477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568, 573-586, 588-590, 592, 706-708, 775, 776, 778 and 780, antibody compositions capable of binding such polypeptides, and numerous additional embodiments employing such compositions, for example in the detection, diagnosis and/or therapy of human prostate cancer.

POLYNUCLEOTIDE COMPOSITIONS

As used herein, the terms "DNA segment" and "polynucleotide" refer to a DNA molecule that has been isolated free of total genomic DNA of a particular species.

Therefore, a DNA segment encoding a polypeptide refers to a DNA segment that contains

- 5 one or more coding sequences yet is substantially isolated away from, or purified free from, total genomic DNA of the species from which the DNA segment is obtained. Included within the terms "DNA segment" and "polynucleotide" are DNA segments and smaller fragments of such segments, and also recombinant vectors, including, for example, plasmids, cosmids, phagemids, phage, viruses, and the like.

10 As will be understood by those skilled in the art, the DNA segments of this invention can include genomic sequences, extra-genomic and plasmid-encoded sequences and smaller engineered gene segments that express, or may be adapted to express, proteins, polypeptides, peptides and the like. Such segments may be naturally isolated, or modified synthetically by the hand of man.

15 "Isolated," as used herein, means that a polynucleotide is substantially away from other coding sequences, and that the DNA segment does not contain large portions of unrelated coding DNA, such as large chromosomal fragments or other functional genes or polypeptide coding regions. Of course, this refers to the DNA segment as originally isolated, and does not exclude genes or coding regions later added to the segment by the
20 hand of man.

As will be recognized by the skilled artisan, polynucleotides may be single-stranded (coding or antisense) or double-stranded, and may be DNA (genomic, cDNA or synthetic) or RNA molecules. RNA molecules include HnRNA molecules, which contain introns and correspond to a DNA molecule in a one-to-one manner, and mRNA molecules,
25 which do not contain introns. Additional coding or non-coding sequences may, but need not, be present within a polynucleotide of the present invention, and a polynucleotide may, but need not, be linked to other molecules and/or support materials.

Polynucleotides may comprise a native sequence (*i.e.*, an endogenous sequence that encodes a prostate-specific protein or a portion thereof) or may comprise a

variant, or a biological or antigenic functional equivalent of such a sequence. Polynucleotide variants may contain one or more substitutions, additions, deletions and/or insertions, as further described below, preferably such that the immunogenicity of the encoded polypeptide is not diminished, relative to a native tumor protein. The effect on the 5 immunogenicity of the encoded polypeptide may generally be assessed as described herein. The term "variants" also encompasses homologous genes of xenogenic origin.

When comparing polynucleotide or polypeptide sequences, two sequences are said to be "identical" if the sequence of nucleotides or amino acids in the two sequences is the same when aligned for maximum correspondence, as described below. Comparisons 10 between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A "comparison window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences 15 are optimally aligned.

Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O. (1978) A model of 20 evolutionary change in proteins – Matrices for detecting distant relationships. In Dayhoff, M.O. (ed.) *Atlas of Protein Sequence and Structure*, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) Unified Approach to Alignment and Phylogenies pp. 626-645 *Methods in Enzymology* vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) *CABIOS* 25 5:151-153; Myers, E.W. and Muller W. (1988) *CABIOS* 4:11-17; Robinson, E.D. (1971) *Comb. Theor* 11:105; Santou, N. Nes, M. (1987) *Mol. Biol. Evol.* 4:406-425; Sneath, P.H.A. and Sokal, R.R. (1973) *Numerical Taxonomy – the Principles and Practice of Numerical Taxonomy*, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) *Proc. Natl. Acad. Sci. USA* 80:726-730.

Alternatively, optimal alignment of sequences for comparison may be conducted by the local identity algorithm of Smith and Waterman (1981) *Add. APL. Math.* 2:482, by the identity alignment algorithm of Needleman and Wunsch (1970) *J. Mol. Biol.* 48:443, by the search for similarity methods of Pearson and Lipman (1988) *Proc. Natl. Acad. Sci. USA* 85: 2444, by computerized implementations of these algorithms (GAP, BESTFIT, BLAST, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group (GCG), 575 Science Dr., Madison, WI), or by inspection.

One preferred example of algorithms that are suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul *et al.* (1977) *Nucl. Acids Res.* 25:3389-3402 and Altschul *et al.* (1990) *J. Mol. Biol.* 215:403-410, respectively. BLAST and BLAST 2.0 can be used, for example with the parameters described herein, to determine percent sequence identity for the polynucleotides and polypeptides of the invention. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information. In one illustrative example, cumulative scores can be calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always >0) and N (penalty score for mismatching residues; always <0). For amino acid sequences, a scoring matrix can be used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a wordlength (W) of 11, and expectation (E) of 10, and the BLOSUM62 scoring matrix (see Henikoff and Henikoff (1989) *Proc. Natl. Acad. Sci. USA* 89:10915) alignments, (B) of 50, expectation (E) of 10, M=5, N=-4 and a comparison of both strands.

Preferably, the “percentage of sequence identity” is determined by comparing two optimally aligned sequences over a window of comparison of at least 20

positions, wherein the portion of the polynucleotide or polypeptide sequence in the comparison window may comprise additions or deletions (*i.e.*, gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The 5 percentage is calculated by determining the number of positions at which the identical nucleic acid bases or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (*i.e.*, the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

10 Therefore, the present invention encompasses polynucleotide and polypeptide sequences having substantial identity to the sequences disclosed herein, for example those comprising at least 50% sequence identity, preferably at least 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% or higher, sequence identity compared to a polynucleotide or polypeptide sequence of this invention using the 15 methods described herein, (*e.g.*, BLAST analysis using standard parameters, as described below). One skilled in this art will recognize that these values can be appropriately adjusted to determine corresponding identity of proteins encoded by two nucleotide sequences by taking into account codon degeneracy, amino acid similarity, reading frame positioning and the like.

20 In additional embodiments, the present invention provides isolated polynucleotides and polypeptides comprising various lengths of contiguous stretches of sequence identical to or complementary to one or more of the sequences disclosed herein. For example, polynucleotides are provided by this invention that comprise at least about 15, 20, 30, 40, 50, 75, 100, 150, 200, 300, 400, 500 or 1000 or more contiguous nucleotides 25 of one or more of the sequences disclosed herein as well as all intermediate lengths there between. It will be readily understood that "intermediate lengths", in this context, means any length between the quoted values, such as 16, 17, 18, 19, *etc.*; 21, 22, 23, *etc.*; 30, 31, 32, *etc.*; 50, 51, 52, 53, *etc.*; 100, 101, 102, 103, *etc.*; 150, 151, 152, 153, *etc.*; including all integers through 200-500; 500-1,000, and the like.

The polynucleotides of the present invention, or fragments thereof, regardless of the length of the coding sequence itself, may be combined with other DNA sequences, such as promoters, polyadenylation signals, additional restriction enzyme sites, multiple cloning sites, other coding segments, and the like, such that their overall length 5 may vary considerably. It is therefore contemplated that a nucleic acid fragment of almost any length may be employed, with the total length preferably being limited by the ease of preparation and use in the intended recombinant DNA protocol. For example, illustrative DNA segments with total lengths of about 10,000, about 5000, about 3000, about 2,000, about 1,000, about 500, about 200, about 100, about 50 base pairs in length, and the like, 10 (including all intermediate lengths) are contemplated to be useful in many implementations of this invention.

In other embodiments, the present invention is directed to polynucleotides that are capable of hybridizing under moderately stringent conditions to a polynucleotide sequence provided herein, or a fragment thereof, or a complementary sequence thereof. 15 Hybridization techniques are well known in the art of molecular biology. For purposes of illustration, suitable moderately stringent conditions for testing the hybridization of a polynucleotide of this invention with other polynucleotides include prewashing in a solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-65°C, 5 X SSC, overnight; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X 20 and 0.2X SSC containing 0.1% SDS.

Moreover, it will be appreciated by those of ordinary skill in the art that, as a result of the degeneracy of the genetic code, there are many nucleotide sequences that encode a polypeptide as described herein. Some of these polynucleotides bear minimal homology to the nucleotide sequence of any native gene. Nonetheless, polynucleotides that 25 vary due to differences in codon usage are specifically contemplated by the present invention. Further, alleles of the genes comprising the polynucleotide sequences provided herein are within the scope of the present invention. Alleles are endogenous genes that are altered as a result of one or more mutations, such as deletions, additions and/or substitutions of nucleotides. The resulting mRNA and protein may, but need not, have an

altered structure or function. Alleles may be identified using standard techniques (such as hybridization, amplification and/or database sequence comparison).

PROBES AND PRIMERS

In other embodiments of the present invention, the polynucleotide sequences provided herein can be advantageously used as probes or primers for nucleic acid hybridization. As such, it is contemplated that nucleic acid segments that comprise a sequence region of at least about 15 nucleotide long contiguous sequence that has the same sequence as, or is complementary to, a 15 nucleotide long contiguous sequence disclosed herein will find particular utility. Longer contiguous identical or complementary sequences, *e.g.*, those of about 20, 30, 40, 50, 100, 200, 500, 1000 (including all intermediate lengths) and even up to full length sequences will also be of use in certain embodiments.

The ability of such nucleic acid probes to specifically hybridize to a sequence of interest will enable them to be of use in detecting the presence of complementary sequences in a given sample. However, other uses are also envisioned, such as the use of the sequence information for the preparation of mutant species primers, or primers for use in preparing other genetic constructions.

Polynucleotide molecules having sequence regions consisting of contiguous nucleotide stretches of 10-14, 15-20, 30, 50, or even of 100-200 nucleotides or so (including intermediate lengths as well), identical or complementary to a polynucleotide sequence disclosed herein, are particularly contemplated as hybridization probes for use in, *e.g.*, Southern and Northern blotting. This would allow a gene product, or fragment thereof, to be analyzed, both in diverse cell types and also in various bacterial cells. The total size of fragment, as well as the size of the complementary stretch(es), will ultimately depend on the intended use or application of the particular nucleic acid segment. Smaller fragments will generally find use in hybridization embodiments, wherein the length of the contiguous complementary region may be varied, such as between about 15 and about 100

nucleotides, but larger contiguous complementarity stretches may be used, according to the length complementary sequences one wishes to detect.

The use of a hybridization probe of about 15-25 nucleotides in length allows the formation of a duplex molecule that is both stable and selective. Molecules having 5 contiguous complementary sequences over stretches greater than 15 bases in length are generally preferred, though, in order to increase stability and selectivity of the hybrid, and thereby improve the quality and degree of specific hybrid molecules obtained. One will generally prefer to design nucleic acid molecules having gene-complementary stretches of 15 to 25 contiguous nucleotides, or even longer where desired.

10 Hybridization probes may be selected from any portion of any of the sequences disclosed herein. All that is required is to review the sequence set forth in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777 and 789, or to any continuous portion of the sequence, 15 from about 15-25 nucleotides in length up to and including the full length sequence, that one wishes to utilize as a probe or primer. The choice of probe and primer sequences may be governed by various factors. For example, one may wish to employ primers from towards the termini of the total sequence.

20 Small polynucleotide segments or fragments may be readily prepared by, for example, directly synthesizing the fragment by chemical means, as is commonly practiced using an automated oligonucleotide synthesizer. Also, fragments may be obtained by application of nucleic acid reproduction technology, such as the PCR™ technology of U. S. Patent 4,683,202 (incorporated herein by reference), by introducing selected sequences into recombinant vectors for recombinant production, and by other recombinant DNA 25 techniques generally known to those of skill in the art of molecular biology.

The nucleotide sequences of the invention may be used for their ability to selectively form duplex molecules with complementary stretches of the entire gene or gene fragments of interest. Depending on the application envisioned, one will typically desire to employ varying conditions of hybridization to achieve varying degrees of selectivity of

probe towards target sequence. For applications requiring high selectivity, one will typically desire to employ relatively stringent conditions to form the hybrids, e.g., one will select relatively low salt and/or high temperature conditions, such as provided by a salt concentration of from about 0.02 M to about 0.15 M salt at temperatures of from about 5 50°C to about 70°C. Such selective conditions tolerate little, if any, mismatch between the probe and the template or target strand, and would be particularly suitable for isolating related sequences.

Of course, for some applications, for example, where one desires to prepare mutants employing a mutant primer strand hybridized to an underlying template, less 10 stringent (reduced stringency) hybridization conditions will typically be needed in order to allow formation of the heteroduplex. In these circumstances, one may desire to employ salt conditions such as those of from about 0.15 M to about 0.9 M salt, at temperatures ranging from about 20°C to about 55°C. Cross-hybridizing species can thereby be readily identified as positively hybridizing signals with respect to control hybridizations. In any 15 case, it is generally appreciated that conditions can be rendered more stringent by the addition of increasing amounts of formamide, which serves to destabilize the hybrid duplex in the same manner as increased temperature. Thus, hybridization conditions can be readily manipulated, and thus will generally be a method of choice depending on the desired results.

20 POLYNUCLEOTIDE IDENTIFICATION AND CHARACTERIZATION

Polynucleotides may be identified, prepared and/or manipulated using any of a variety of well established techniques. For example, a polynucleotide may be identified, as described in more detail below, by screening a microarray of cDNAs for tumor-associated expression (*i.e.*, expression that is at least two fold greater in a tumor than 25 in normal tissue, as determined using a representative assay provided herein). Such screens may be performed, for example, using a Synteni microarray (Palo Alto, CA) according to the manufacturer's instructions (and essentially as described by Schena *et al.*, *Proc. Natl. Acad. Sci. USA* 93:10614-10619, 1996 and Heller *et al.*, *Proc. Natl. Acad. Sci. USA*

94:2150-2155, 1997). Alternatively, polynucleotides may be amplified from cDNA prepared from cells expressing the proteins described herein, such as prostate-specific cells. Such polynucleotides may be amplified via polymerase chain reaction (PCR). For this approach, sequence-specific primers may be designed based on the sequences provided 5 herein, and may be purchased or synthesized.

An amplified portion of a polynucleotide of the present invention may be used to isolate a full length gene from a suitable library (e.g., a prostate tumor cDNA library) using well known techniques. Within such techniques, a library (cDNA or genomic) is screened using one or more polynucleotide probes or primers suitable for 10 amplification. Preferably, a library is size-selected to include larger molecules. Random primed libraries may also be preferred for identifying 5' and upstream regions of genes. Genomic libraries are preferred for obtaining introns and extending 5' sequences.

For hybridization techniques, a partial sequence may be labeled (e.g., by nick-translation or end-labeling with ^{32}P) using well known techniques. A bacterial or 15 bacteriophage library is then generally screened by hybridizing filters containing denatured bacterial colonies (or lawns containing phage plaques) with the labeled probe (see Sambrook *et al.*, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989). Hybridizing colonies or plaques are selected and expanded, and the DNA is isolated for further analysis. cDNA clones may be 20 analyzed to determine the amount of additional sequence by, for example, PCR using a primer from the partial sequence and a primer from the vector. Restriction maps and partial sequences may be generated to identify one or more overlapping clones. The complete sequence may then be determined using standard techniques, which may involve generating a series of deletion clones. The resulting overlapping sequences can then 25 assembled into a single contiguous sequence. A full length cDNA molecule can be generated by ligating suitable fragments, using well known techniques.

Alternatively, there are numerous amplification techniques for obtaining a full length coding sequence from a partial cDNA sequence. Within such techniques, amplification is generally performed via PCR. Any of a variety of commercially available

kits may be used to perform the amplification step. Primers may be designed using, for example, software well known in the art. Primers are preferably 22-30 nucleotides in length, have a GC content of at least 50% and anneal to the target sequence at temperatures of about 68°C to 72°C. The amplified region may be sequenced as described above, and 5 overlapping sequences assembled into a contiguous sequence.

One such amplification technique is inverse PCR (*see Triglia et al., Nucl. Acids Res. 16:8186, 1988*), which uses restriction enzymes to generate a fragment in the known region of the gene. The fragment is then circularized by intramolecular ligation and used as a template for PCR with divergent primers derived from the known region. Within 10 an alternative approach, sequences adjacent to a partial sequence may be retrieved by amplification with a primer to a linker sequence and a primer specific to a known region. The amplified sequences are typically subjected to a second round of amplification with the same linker primer and a second primer specific to the known region. A variation on this procedure, which employs two primers that initiate extension in opposite directions from 15 the known sequence, is described in WO 96/38591. Another such technique is known as "rapid amplification of cDNA ends" or RACE. This technique involves the use of an internal primer and an external primer, which hybridizes to a polyA region or vector sequence, to identify sequences that are 5' and 3' of a known sequence. Additional techniques include capture PCR (*Lagerstrom et al., PCR Methods Applic. 1:111-19, 1991*) 20 and walking PCR (*Parker et al., Nucl. Acids. Res. 19:3055-60, 1991*). Other methods employing amplification may also be employed to obtain a full length cDNA sequence.

In certain instances, it is possible to obtain a full length cDNA sequence by analysis of sequences provided in an expressed sequence tag (EST) database, such as that available from GenBank. Searches for overlapping ESTs may generally be performed 25 using well known programs (*e.g., NCBI BLAST searches*), and such ESTs may be used to generate a contiguous full length sequence. Full length DNA sequences may also be obtained by analysis of genomic fragments.

POLYNUCLEOTIDE EXPRESSION IN HOST CELLS

In other embodiments of the invention, polynucleotide sequences or fragments thereof which encode polypeptides of the invention, or fusion proteins or functional equivalents thereof, may be used in recombinant DNA molecules to direct expression of a polypeptide in appropriate host cells. Due to the inherent degeneracy of the genetic code, other DNA sequences that encode substantially the same or a functionally equivalent amino acid sequence may be produced and these sequences may be used to clone and express a given polypeptide.

As will be understood by those of skill in the art, it may be advantageous in some instances to produce polypeptide-encoding nucleotide sequences possessing non-naturally occurring codons. For example, codons preferred by a particular prokaryotic or eukaryotic host can be selected to increase the rate of protein expression or to produce a recombinant RNA transcript having desirable properties, such as a half-life which is longer than that of a transcript generated from the naturally occurring sequence.

Moreover, the polynucleotide sequences of the present invention can be engineered using methods generally known in the art in order to alter polypeptide encoding sequences for a variety of reasons, including but not limited to, alterations which modify the cloning, processing, and/or expression of the gene product. For example, DNA shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic oligonucleotides may be used to engineer the nucleotide sequences. In addition, site-directed mutagenesis may be used to insert new restriction sites, alter glycosylation patterns, change codon preference, produce splice variants, or introduce mutations, and so forth.

In another embodiment of the invention, natural, modified, or recombinant nucleic acid sequences may be ligated to a heterologous sequence to encode a fusion protein. For example, to screen peptide libraries for inhibitors of polypeptide activity, it may be useful to encode a chimeric protein that can be recognized by a commercially available antibody. A fusion protein may also be engineered to contain a cleavage site

located between the polypeptide-encoding sequence and the heterologous protein sequence, so that the polypeptide may be cleaved and purified away from the heterologous moiety.

Sequences encoding a desired polypeptide may be synthesized, in whole or in part, using chemical methods well known in the art (see Caruthers, M. H. *et al.* (1980)

- 5 *Nucl. Acids Res. Symp. Ser.* 215-223, Horn, T. *et al.* (1980) *Nucl. Acids Res. Symp. Ser.* 225-232). Alternatively, the protein itself may be produced using chemical methods to synthesize the amino acid sequence of a polypeptide, or a portion thereof. For example, peptide synthesis can be performed using various solid-phase techniques (Roberge, J. Y. *et al.* (1995) *Science* 269:202-204) and automated synthesis may be achieved, for example,
- 10 using the ABI 431A Peptide Synthesizer (Perkin Elmer, Palo Alto, CA).

A newly synthesized peptide may be substantially purified by preparative high performance liquid chromatography (*e.g.*, Creighton, T. (1983) *Proteins, Structures and Molecular Principles*, WH Freeman and Co., New York, N.Y.) or other comparable techniques available in the art. The composition of the synthetic peptides may be confirmed by amino acid analysis or sequencing (*e.g.*, the Edman degradation procedure). Additionally, the amino acid sequence of a polypeptide, or any part thereof, may be altered during direct synthesis and/or combined using chemical methods with sequences from other proteins, or any part thereof, to produce a variant polypeptide.

- In order to express a desired polypeptide, the nucleotide sequences encoding
- 20 the polypeptide, or functional equivalents, may be inserted into appropriate expression vector, *i.e.*, a vector which contains the necessary elements for the transcription and translation of the inserted coding sequence. Methods which are well known to those skilled in the art may be used to construct expression vectors containing sequences encoding a polypeptide of interest and appropriate transcriptional and translational control
- 25 elements. These methods include in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. Such techniques are described in Sambrook, J. *et al.* (1989) *Molecular Cloning, A Laboratory Manual*, Cold Spring Harbor Press, Plainview, N.Y., and Ausubel, F. M. *et al.* (1989) *Current Protocols in Molecular Biology*, John Wiley & Sons, New York. N.Y.

A variety of expression vector/host systems may be utilized to contain and express polynucleotide sequences. These include, but are not limited to, microorganisms such as bacteria transformed with recombinant bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems 5 infected with virus expression vectors (e.g., baculovirus); plant cell systems transformed with virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or with bacterial expression vectors (e.g., Ti or pBR322 plasmids); or animal cell systems.

The "control elements" or "regulatory sequences" present in an expression 10 vector are those non-translated regions of the vector--enhancers, promoters, 5' and 3' untranslated regions--which interact with host cellular proteins to carry out transcription and translation. Such elements may vary in their strength and specificity. Depending on the vector system and host utilized, any number of suitable transcription and translation elements, including constitutive and inducible promoters, may be used. For example, when 15 cloning in bacterial systems, inducible promoters such as the hybrid lacZ promoter of the PBLUESCRIPT phagemid (Stratagene, La Jolla, Calif.) or PSPORT1 plasmid (Gibco BRL, Gaithersburg, MD) and the like may be used. In mammalian cell systems, promoters from mammalian genes or from mammalian viruses are generally preferred. If it is necessary to generate a cell line that contains multiple copies of the sequence encoding a polypeptide, 20 vectors based on SV40 or EBV may be advantageously used with an appropriate selectable marker.

In bacterial systems, a number of expression vectors may be selected depending upon the use intended for the expressed polypeptide. For example, when large quantities are needed, for example for the induction of antibodies, vectors which direct 25 high level expression of fusion proteins that are readily purified may be used. Such vectors include, but are not limited to, the multifunctional *E. coli* cloning and expression vectors such as BLUESCRIPT (Stratagene), in which the sequence encoding the polypeptide of interest may be ligated into the vector in frame with sequences for the amino-terminal Met and the subsequent 7 residues of .beta.-galactosidase so that a hybrid protein is produced;

pIN vectors (Van Heeke, G. and S. M. Schuster (1989) *J. Biol. Chem.* 264:5503-5509); and the like. pGEX Vectors (Promega, Madison, Wis.) may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption to 5 glutathione-agarose beads followed by elution in the presence of free glutathione. Proteins made in such systems may be designed to include heparin, thrombin, or factor XA protease cleavage sites so that the cloned polypeptide of interest can be released from the GST moiety at will.

In the yeast, *Saccharomyces cerevisiae*, a number of vectors containing 10 constitutive or inducible promoters such as alpha factor, alcohol oxidase, and PGH may be used. For reviews, see Ausubel *et al.* (supra) and Grant *et al.* (1987) *Methods Enzymol.* 153:516-544.

In cases where plant expression vectors are used, the expression of sequences encoding polypeptides may be driven by any of a number of promoters. For 15 example, viral promoters such as the 35S and 19S promoters of CaMV may be used alone or in combination with the omega leader sequence from TMV (Takamatsu, N. (1987) *EMBO J.* 6:307-311. Alternatively, plant promoters such as the small subunit of RUBISCO or heat shock promoters may be used (Coruzzi, G. *et al.* (1984) *EMBO J.* 3:1671-1680; Broglie, R. *et al.* (1984) *Science* 224:838-843; and Winter, J. *et al.* (1991) *Results Probl. 20 Cell Differ.* 17:85-105). These constructs can be introduced into plant cells by direct DNA transformation or pathogen-mediated transfection. Such techniques are described in a number of generally available reviews (see, for example, Hobbs, S. or Murry, L. E. in McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York, N.Y.; pp. 191-196).

25 An insect system may also be used to express a polypeptide of interest. For example, in one such system, *Autographa californica* nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes in *Spodoptera frugiperda* cells or in *Trichoplusia* larvae. The sequences encoding the polypeptide may be cloned into a non-essential region of the virus, such as the polyhedrin gene, and placed under control of the

polyhedrin promoter. Successful insertion of the polypeptide-encoding sequence will render the polyhedrin gene inactive and produce recombinant virus lacking coat protein. The recombinant viruses may then be used to infect, for example, *S. frugiperda* cells or *Trichoplusia* larvae in which the polypeptide of interest may be expressed (Engelhard, E. K. et al. (1994) *Proc. Natl. Acad. Sci.* 91 :3224-3227).

In mammalian host cells, a number of viral-based expression systems are generally available. For example, in cases where an adenovirus is used as an expression vector, sequences encoding a polypeptide of interest may be ligated into an adenovirus transcription/translation complex consisting of the late promoter and tripartite leader sequence. Insertion in a non-essential E1 or E3 region of the viral genome may be used to obtain a viable virus which is capable of expressing the polypeptide in infected host cells (Logan, J. and Shenk, T. (1984) *Proc. Natl. Acad. Sci.* 81:3655-3659). In addition, transcription enhancers, such as the Rous sarcoma virus (RSV) enhancer, may be used to increase expression in mammalian host cells.

Specific initiation signals may also be used to achieve more efficient translation of sequences encoding a polypeptide of interest. Such signals include the ATG initiation codon and adjacent sequences. In cases where sequences encoding the polypeptide, its initiation codon, and upstream sequences are inserted into the appropriate expression vector, no additional transcriptional or translational control signals may be needed. However, in cases where only coding sequence, or a portion thereof, is inserted, exogenous translational control signals including the ATG initiation codon should be provided. Furthermore, the initiation codon should be in the correct reading frame to ensure translation of the entire insert. Exogenous translational elements and initiation codons may be of various origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of enhancers which are appropriate for the particular cell system which is used, such as those described in the literature (Scharf, D. et al. (1994) *Results Probl. Cell Differ.* 20:125-162).

In addition, a host cell strain may be chosen for its ability to modulate the expression of the inserted sequences or to process the expressed protein in the desired

fashion. Such modifications of the polypeptide include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation, and acylation. Post-translational processing which cleaves a "pro" form of the protein may also be used to facilitate correct insertion, folding and/or function. Different host cells such as CHO, HeLa, MDCK, 5 HEK293, and WI38, which have specific cellular machinery and characteristic mechanisms for such post-translational activities, may be chosen to ensure the correct modification and processing of the foreign protein.

For long-term, high-yield production of recombinant proteins, stable expression is generally preferred. For example, cell lines which stably express a 10 polynucleotide of interest may be transformed using expression vectors which may contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector. Following the introduction of the vector, cells may be allowed to grow for 1-2 days in an enriched media before they are switched to selective media. The purpose of the selectable marker is to confer resistance to selection, 15 and its presence allows growth and recovery of cells which successfully express the introduced sequences. Resistant clones of stably transformed cells may be proliferated using tissue culture techniques appropriate to the cell type.

Any number of selection systems may be used to recover transformed cell lines. These include, but are not limited to, the herpes simplex virus thymidine kinase 20 (Wigler, M. et al. (1977) *Cell* 11:223-32) and adenine phosphoribosyltransferase (Lowy, I. et al. (1990) *Cell* 22:817-23) genes which can be employed in tk.sup.- or aprt.sup.- cells, respectively. Also, antimetabolite, antibiotic or herbicide resistance can be used as the basis for selection; for example, dhfr which confers resistance to methotrexate (Wigler, M. et al. (1980) *Proc. Natl. Acad. Sci.* 77:3567-70); npt, which confers resistance to the 25 aminoglycosides, neomycin and G-418 (Colbere-Garapin, F. et al (1981) *J. Mol. Biol.* 150:1-14); and als or pat, which confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively (Murry, *supra*). Additional selectable genes have been described, for example, trpB, which allows cells to utilize indole in place of tryptophan, or hisD, which allows cells to utilize histinol in place of histidine (Hartman, S. C. and R. C.

Mulligan (1988) *Proc. Natl. Acad. Sci.* 85:8047-51). Recently, the use of visible markers has gained popularity with such markers as anthocyanins, beta-glucuronidase and its substrate GUS, and luciferase and its substrate luciferin, being widely used not only to identify transformants, but also to quantify the amount of transient or stable protein expression attributable to a specific vector system (Rhodes, C. A. *et al.* (1995) *Methods Mol. Biol.* 55:121-131).

Although the presence/absence of marker gene expression suggests that the gene of interest is also present, its presence and expression may need to be confirmed. For example, if the sequence encoding a polypeptide is inserted within a marker gene sequence, 10 recombinant cells containing sequences can be identified by the absence of marker gene function. Alternatively, a marker gene can be placed in tandem with a polypeptide-encoding sequence under the control of a single promoter. Expression of the marker gene in response to induction or selection usually indicates expression of the tandem gene as well.

15 Alternatively, host cells which contain and express a desired polynucleotide sequence may be identified by a variety of procedures known to those of skill in the art. These procedures include, but are not limited to, DNA-DNA or DNA-RNA hybridizations and protein bioassay or immunoassay techniques which include membrane, solution, or chip based technologies for the detection and/or quantification of nucleic acid or protein.

20 A variety of protocols for detecting and measuring the expression of polynucleotide-encoded products, using either polyclonal or monoclonal antibodies specific for the product are known in the art. Examples include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), and fluorescence activated cell sorting (FACS). A two-site, monoclonal-based immunoassay utilizing monoclonal 25 antibodies reactive to two non-interfering epitopes on a given polypeptide may be preferred for some applications, but a competitive binding assay may also be employed. These and other assays are described, among other places, in Hampton, R. *et al.* (1990; Serological Methods, a Laboratory Manual, APS Press, St Paul. Minn.) and Maddox, D. E. *et al.* (1983; *J. Exp. Med.* 158:1211-1216).

A wide variety of labels and conjugation techniques are known by those skilled in the art and may be used in various nucleic acid and amino acid assays. Means for producing labeled hybridization or PCR probes for detecting sequences related to polynucleotides include oligolabeling, nick translation, end-labeling or PCR amplification 5 using a labeled nucleotide. Alternatively, the sequences, or any portions thereof may be cloned into a vector for the production of an mRNA probe. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by addition of an appropriate RNA polymerase such as T7, T3, or SP6 and labeled nucleotides. These procedures may be conducted using a variety of commercially available 10 kits. Suitable reporter molecules or labels, which may be used include radionuclides, enzymes, fluorescent, chemiluminescent, or chromogenic agents as well as substrates, cofactors, inhibitors, magnetic particles, and the like.

Host cells transformed with a polynucleotide sequence of interest may be cultured under conditions suitable for the expression and recovery of the protein from cell 15 culture. The protein produced by a recombinant cell may be secreted or contained intracellularly depending on the sequence and/or the vector used. As will be understood by those of skill in the art, expression vectors containing polynucleotides of the invention may be designed to contain signal sequences which direct secretion of the encoded polypeptide through a prokaryotic or eukaryotic cell membrane. Other recombinant constructions may 20 be used to join sequences encoding a polypeptide of interest to nucleotide sequence encoding a polypeptide domain which will facilitate purification of soluble proteins. Such purification facilitating domains include, but are not limited to, metal chelating peptides such as histidine-tryptophan modules that allow purification on immobilized metals, protein A domains that allow purification on immobilized immunoglobulin, and the domain 25 utilized in the FLAGS extension/affinity purification system (Immunex Corp., Seattle, Wash.). The inclusion of cleavable linker sequences such as those specific for Factor XA or enterokinase (Invitrogen. San Diego, Calif.) between the purification domain and the encoded polypeptide may be used to facilitate purification. One such expression vector provides for expression of a fusion protein containing a polypeptide of interest and a

nucleic acid encoding 6 histidine residues preceding a thioredoxin or an enterokinase cleavage site. The histidine residues facilitate purification on IMIAC (immobilized metal ion affinity chromatography) as described in Porath, J. *et al.* (1992, *Prot. Exp. Purif.* 3:263-281) while the enterokinase cleavage site provides a means for purifying the desired 5 polypeptide from the fusion protein. A discussion of vectors which contain fusion proteins is provided in Kroll, D. J. *et al.* (1993; *DNA Cell Biol.* 12:441-453).

In addition to recombinant production methods, polypeptides of the invention, and fragments thereof, may be produced by direct peptide synthesis using solid-phase techniques (Merrifield J. (1963) *J. Am. Chem. Soc.* 85:2149-2154). Protein synthesis 10 may be performed using manual techniques or by automation. Automated synthesis may be achieved, for example, using Applied Biosystems 431A Peptide Synthesizer (Perkin Elmer). Alternatively, various fragments may be chemically synthesized separately and combined using chemical methods to produce the full length molecule.

SITE-SPECIFIC MUTAGENESIS

Site-specific mutagenesis is a technique useful in the preparation of individual peptides, or biologically functional equivalent polypeptides, through specific mutagenesis of the underlying polynucleotides that encode them. The technique, well-known to those of skill in the art, further provides a ready ability to prepare and test sequence variants, for example, incorporating one or more of the foregoing considerations, 15 by introducing one or more nucleotide sequence changes into the DNA. Site-specific mutagenesis allows the production of mutants through the use of specific oligonucleotide sequences which encode the DNA sequence of the desired mutation, as well as a sufficient number of adjacent nucleotides, to provide a primer sequence of sufficient size and sequence complexity to form a stable duplex on both sides of the deletion junction being 20 traversed. Mutations may be employed in a selected polynucleotide sequence to improve, alter, decrease, modify, or otherwise change the properties of the polynucleotide itself, and/or alter the properties, activity, composition, stability, or primary sequence of the 25 encoded polypeptide.

In certain embodiments of the present invention, the inventors contemplate the mutagenesis of the disclosed polynucleotide sequences to alter one or more properties of the encoded polypeptide, such as the antigenicity of a polypeptide vaccine. The techniques of site-specific mutagenesis are well-known in the art, and are widely used to 5 create variants of both polypeptides and polynucleotides. For example, site-specific mutagenesis is often used to alter a specific portion of a DNA molecule. In such embodiments, a primer comprising typically about 14 to about 25 nucleotides or so in length is employed, with about 5 to about 10 residues on both sides of the junction of the sequence being altered.

10 As will be appreciated by those of skill in the art, site-specific mutagenesis techniques have often employed a phage vector that exists in both a single stranded and double stranded form. Typical vectors useful in site-directed mutagenesis include vectors such as the M13 phage. These phage are readily commercially-available and their use is generally well-known to those skilled in the art. Double-stranded plasmids are also 15 routinely employed in site directed mutagenesis that eliminates the step of transferring the gene of interest from a plasmid to a phage.

In general, site-directed mutagenesis in accordance herewith is performed by first obtaining a single-stranded vector or melting apart of two strands of a double-stranded vector that includes within its sequence a DNA sequence that encodes the 20 desired peptide. An oligonucleotide primer bearing the desired mutated sequence is prepared, generally synthetically. This primer is then annealed with the single-stranded vector, and subjected to DNA polymerizing enzymes such as *E. coli* polymerase I Klenow fragment, in order to complete the synthesis of the mutation-bearing strand. Thus, a heteroduplex is formed wherein one strand encodes the original non-mutated sequence and 25 the second strand bears the desired mutation. This heteroduplex vector is then used to transform appropriate cells, such as *E. coli* cells, and clones are selected which include recombinant vectors bearing the mutated sequence arrangement.

The preparation of sequence variants of the selected peptide-encoding DNA segments using site-directed mutagenesis provides a means of producing potentially useful

species and is not meant to be limiting as there are other ways in which sequence variants of peptides and the DNA sequences encoding them may be obtained. For example, recombinant vectors encoding the desired peptide sequence may be treated with mutagenic agents, such as hydroxylamine, to obtain sequence variants. Specific details regarding 5 these methods and protocols are found in the teachings of Maloy *et al.*, 1994; Segal, 1976; Prokop and Bajpai, 1991; Kuby, 1994; and Maniatis *et al.*, 1982, each incorporated herein by reference, for that purpose.

As used herein, the term "oligonucleotide directed mutagenesis procedure" refers to template-dependent processes and vector-mediated propagation which result in an 10 increase in the concentration of a specific nucleic acid molecule relative to its initial concentration, or in an increase in the concentration of a detectable signal, such as amplification. As used herein, the term "oligonucleotide directed mutagenesis procedure" is intended to refer to a process that involves the template-dependent extension of a primer 15 molecule. The term template dependent process refers to nucleic acid synthesis of an RNA or a DNA molecule wherein the sequence of the newly synthesized strand of nucleic acid is dictated by the well-known rules of complementary base pairing (see, for example, Watson, 1987). Typically, vector mediated methodologies involve the introduction of the nucleic acid fragment into a DNA or RNA vector, the clonal amplification of the vector, and the recovery of the amplified nucleic acid fragment. Examples of such methodologies 20 are provided by U. S. Patent No. 4,237,224, specifically incorporated herein by reference in its entirety.

POLYNUCLEOTIDE AMPLIFICATION TECHNIQUES

A number of template dependent processes are available to amplify the target sequences of interest present in a sample. One of the best known amplification 25 methods is the polymerase chain reaction (PCRTM) which is described in detail in U.S. Patent Nos. 4,683,195, 4,683,202 and 4,800,159, each of which is incorporated herein by reference in its entirety. Briefly, in PCRTM, two primer sequences are prepared which are complementary to regions on opposite complementary strands of the target sequence. An

excess of deoxynucleoside triphosphates is added to a reaction mixture along with a DNA polymerase (e.g., *Taq* polymerase). If the target sequence is present in a sample, the primers will bind to the target and the polymerase will cause the primers to be extended along the target sequence by adding on nucleotides. By raising and lowering the
5 temperature of the reaction mixture, the extended primers will dissociate from the target to form reaction products, excess primers will bind to the target and to the reaction product and the process is repeated. Preferably reverse transcription and PCR™ amplification procedure may be performed in order to quantify the amount of mRNA amplified. Polymerase chain reaction methodologies are well known in the art.

10 Another method for amplification is the ligase chain reaction (referred to as LCR), disclosed in Eur. Pat. Appl. Publ. No. 320,308 (specifically incorporated herein by reference in its entirety). In LCR, two complementary probe pairs are prepared, and in the presence of the target sequence, each pair will bind to opposite complementary strands of the target such that they abut. In the presence of a ligase, the two probe pairs will link to
15 form a single unit. By temperature cycling, as in PCR™, bound ligated units dissociate from the target and then serve as "target sequences" for ligation of excess probe pairs. U.S. Patent No. 4,883,750, incorporated herein by reference in its entirety, describes an alternative method of amplification similar to LCR for binding probe pairs to a target sequence.

20 Qbeta Replicase, described in PCT Intl. Pat. Appl. Publ. No. PCT/US87/00880, incorporated herein by reference in its entirety, may also be used as still another amplification method in the present invention. In this method, a replicative sequence of RNA that has a region complementary to that of a target is added to a sample in the presence of an RNA polymerase. The polymerase will copy the replicative sequence
25 that can then be detected.

An isothermal amplification method, in which restriction endonucleases and ligases are used to achieve the amplification of target molecules that contain nucleotide 5'-[α -thio]triphosphates in one strand of a restriction site (Walker *et al.*, 1992, incorporated

herein by reference in its entirety), may also be useful in the amplification of nucleic acids in the present invention.

Strand Displacement Amplification (SDA) is another method of carrying out isothermal amplification of nucleic acids which involves multiple rounds of strand displacement and synthesis, *i.e.* nick translation. A similar method, called Repair Chain Reaction (RCR) is another method of amplification which may be useful in the present invention and is involves annealing several probes throughout a region targeted for amplification, followed by a repair reaction in which only two of the four bases are present. The other two bases can be added as biotinylated derivatives for easy detection. A similar approach is used in SDA.

Sequences can also be detected using a cyclic probe reaction (CPR). In CPR, a probe having a 3' and 5' sequences of non-target DNA and an internal or "middle" sequence of the target protein specific RNA is hybridized to DNA which is present in a sample. Upon hybridization, the reaction is treated with RNaseH, and the products of the probe are identified as distinctive products by generating a signal that is released after digestion. The original template is annealed to another cycling probe and the reaction is repeated. Thus, CPR involves amplifying a signal generated by hybridization of a probe to a target gene specific expressed nucleic acid.

Still other amplification methods described in Great Britain Pat. Appl. No. 2 202 328, and in PCT Intl. Pat. Appl. Publ. No. PCT/US89/01025, each of which is incorporated herein by reference in its entirety, may be used in accordance with the present invention. In the former application, "modified" primers are used in a PCR-like, template and enzyme dependent synthesis. The primers may be modified by labeling with a capture moiety (*e.g.*, biotin) and/or a detector moiety (*e.g.*, enzyme). In the latter application, an excess of labeled probes is added to a sample. In the presence of the target sequence, the probe binds and is cleaved catalytically. After cleavage, the target sequence is released intact to be bound by excess probe. Cleavage of the labeled probe signals the presence of the target sequence.

Other nucleic acid amplification procedures include transcription-based amplification systems (TAS) (Kwoh *et al.*, 1989; PCT Intl. Pat. Appl. Publ. No. WO 88/10315, incorporated herein by reference in its entirety), including nucleic acid sequence based amplification (NASBA) and 3SR. In NASBA, the nucleic acids can be prepared for 5 amplification by standard phenol/chloroform extraction, heat denaturation of a sample, treatment with lysis buffer and minispin columns for isolation of DNA and RNA or guanidinium chloride extraction of RNA. These amplification techniques involve annealing a primer that has sequences specific to the target sequence. Following polymerization, DNA/RNA hybrids are digested with RNase H while double stranded 10 DNA molecules are heat-denatured again. In either case the single stranded DNA is made fully double stranded by addition of second target-specific primer, followed by polymerization. The double stranded DNA molecules are then multiply transcribed by a polymerase such as T7 or SP6. In an isothermal cyclic reaction, the RNAs are reverse transcribed into DNA, and transcribed once again with a polymerase such as T7 or SP6. 15 The resulting products, whether truncated or complete, indicate target-specific sequences.

Eur. Pat. Appl. Publ. No. 329,822, incorporated herein by reference in its entirety, disclose a nucleic acid amplification process involving cyclically synthesizing single-stranded RNA ("ssRNA"), ssDNA, and double-stranded DNA (dsDNA), which may be used in accordance with the present invention. The ssRNA is a first template for a first 20 primer oligonucleotide, which is elongated by reverse transcriptase (RNA-dependent DNA polymerase). The RNA is then removed from resulting DNA:RNA duplex by the action of ribonuclease H (RNase H, an RNase specific for RNA in a duplex with either DNA or RNA). The resultant ssDNA is a second template for a second primer, which also includes the sequences of an RNA polymerase promoter (exemplified by T7 RNA polymerase) 5' to 25 its homology to its template. This primer is then extended by DNA polymerase (exemplified by the large "Klenow" fragment of *E. coli* DNA polymerase I), resulting as a double-stranded DNA ("dsDNA") molecule, having a sequence identical to that of the original RNA between the primers and having additionally, at one end, a promoter sequence. This promoter sequence can be used by the appropriate RNA polymerase to

make many RNA copies of the DNA. These copies can then re-enter the cycle leading to very swift amplification. With proper choice of enzymes, this amplification can be done isothermally without addition of enzymes at each cycle. Because of the cyclical nature of this process, the starting sequence can be chosen to be in the form of either DNA or RNA.

5 PCT Intl. Pat. Appl. Publ. No. WO 89/06700, incorporated herein by reference in its entirety, disclose a nucleic acid sequence amplification scheme based on the hybridization of a promoter/primer sequence to a target single-stranded DNA ("ssDNA") followed by transcription of many RNA copies of the sequence. This scheme is not cyclic; *i.e.* new templates are not produced from the resultant RNA transcripts. Other
10 amplification methods include "RACE" (Frohman, 1990), and "one-sided PCR" (Ohara, 1989) which are well-known to those of skill in the art.

Methods based on ligation of two (or more) oligonucleotides in the presence of nucleic acid having the sequence of the resulting "di-oligonucleotide", thereby amplifying the di-oligonucleotide (Wu and Dean, 1996, incorporated herein by reference in
15 its entirety), may also be used in the amplification of DNA sequences of the present invention.

BIOLOGICAL FUNCTIONAL EQUIVALENTS

Modification and changes may be made in the structure of the polynucleotides and polypeptides of the present invention and still obtain a functional
20 molecule that encodes a polypeptide with desirable characteristics. As mentioned above, it is often desirable to introduce one or more mutations into a specific polynucleotide sequence. In certain circumstances, the resulting encoded polypeptide sequence is altered by this mutation, or in other cases, the sequence of the polypeptide is unchanged by one or more mutations in the encoding polynucleotide.

25 When it is desirable to alter the amino acid sequence of a polypeptide to create an equivalent, or even an improved, second-generation molecule, the amino acid changes may be achieved by changing one or more of the codons of the encoding DNA sequence, according to Table 1.

For example, certain amino acids may be substituted for other amino acids in a protein structure without appreciable loss of interactive binding capacity with structures such as, for example, antigen-binding regions of antibodies or binding sites on substrate molecules. Since it is the interactive capacity and nature of a protein that defines
5 that protein's biological functional activity, certain amino acid sequence substitutions can be made in a protein sequence, and, of course, its underlying DNA coding sequence, and nevertheless obtain a protein with like properties. It is thus contemplated by the inventors that various changes may be made in the peptide sequences of the disclosed compositions, or corresponding DNA sequences which encode said peptides without appreciable loss of
10 their biological utility or activity.

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TABLE 1

Amino Acids		Codons						
Alanine	Ala	A	GCA	GCC	GCG	GCU		
Cysteine	Cys	C	UGC	UGU				
Aspartic acid	Asp	D	GAC	GAU				
Glutamic acid	Glu	E	GAA	GAG				
Phenylalanine	Phe	F	UUC	UUU				
Glycine	Gly	G	GGA	GGC	GGG	GGU		
Histidine	His	H	CAC	CAU				
Isoleucine	Ile	I	AUA	AUC	AUU			
Lysine	Lys	K	AAA	AAG				
Leucine	Leu	L	UUA	UUG	CUA	CUC	CUG	CUU
Methionine	Met	M	AUG					
Asparagine	Asn	N	AAC	AAU				
Proline	Pro	P	CCA	CCC	CCG	CCU		
Glutamine	Gln	Q	CAA	CAG				
Arginine	Arg	R	AGA	AGG	CGA	CGC	CGG	CGU
Serine	Ser	S	AGC	AGU	UCA	UCC	UCG	UCU
Threonine	Thr	T	ACA	ACC	ACG	ACU		
Valine	Val	V	GU	GUC	GUG	GUU		
Tryptophan	Trp	W	UGG					
Tyrosine	Tyr	Y	UAC	UAU				

In making such changes, the hydropathic index of amino acids may be considered. The importance of the hydropathic amino acid index in conferring interactive biologic function on a protein is generally understood in the art (Kyte and Doolittle, 1982, incorporated herein by reference). It is accepted that the relative hydropathic character of the amino acid contributes to the secondary structure of the resultant protein, which in turn defines the interaction of the protein with other molecules, for example, enzymes, substrates, receptors, DNA, antibodies, antigens, and the like. Each amino acid has been

assigned a hydropathic index on the basis of its hydrophobicity and charge characteristics (Kyte and Doolittle, 1982). These values are: isoleucine (+4.5); valine (+4.2); leucine (+3.8); phenylalanine (+2.8); cysteine/cystine (+2.5); methionine (+1.9); alanine (+1.8); glycine (-0.4); threonine (-0.7); serine (-0.8); tryptophan (-0.9); tyrosine (-1.3); proline (-5 1.6); histidine (-3.2); glutamate (-3.5); glutamine (-3.5); aspartate (-3.5); asparagine (-3.5); lysine (-3.9); and arginine (-4.5).

It is known in the art that certain amino acids may be substituted by other amino acids having a similar hydropathic index or score and still result in a protein with similar biological activity, *i.e.* still obtain a biological functionally equivalent protein. In 10 making such changes, the substitution of amino acids whose hydropathic indices are within ± 2 is preferred, those within ± 1 are particularly preferred, and those within ± 0.5 are even more particularly preferred. It is also understood in the art that the substitution of like amino acids can be made effectively on the basis of hydrophilicity. U. S. Patent 4,554,101 (specifically incorporated herein by reference in its entirety), states that the greatest local 15 average hydrophilicity of a protein, as governed by the hydrophilicity of its adjacent amino acids, correlates with a biological property of the protein.

As detailed in U. S. Patent 4,554,101, the following hydrophilicity values have been assigned to amino acid residues: arginine (+3.0); lysine (+3.0); aspartate (+3.0 \pm 1); glutamate (+3.0 \pm 1); serine (+0.3); asparagine (+0.2); glutamine (+0.2); glycine (0); 20 threonine (-0.4); proline (-0.5 \pm 1); alanine (-0.5); histidine (-0.5); cysteine (-1.0); methionine (-1.3); valine (-1.5); leucine (-1.8); isoleucine (-1.8); tyrosine (-2.3); phenylalanine (-2.5); tryptophan (-3.4). It is understood that an amino acid can be substituted for another having a similar hydrophilicity value and still obtain a biologically equivalent, and in particular, an immunologically equivalent protein. In such changes, the 25 substitution of amino acids whose hydrophilicity values are within ± 2 is preferred, those within ± 1 are particularly preferred, and those within ± 0.5 are even more particularly preferred.

As outlined above, amino acid substitutions are generally therefore based on the relative similarity of the amino acid side-chain substituents, for example, their

hydrophobicity, hydrophilicity, charge, size, and the like. Exemplary substitutions that take various of the foregoing characteristics into consideration are well known to those of skill in the art and include: arginine and lysine; glutamate and aspartate; serine and threonine; glutamine and asparagine; and valine, leucine and isoleucine.

5 In addition, any polynucleotide may be further modified to increase stability *in vivo*. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends; the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages in the backbone; and/or the inclusion of nontraditional bases such as inosine, queosine and wybutoxine, as well as acetyl-, methyl-, thio- and other
10 modified forms of adenine, cytidine, guanine, thymine and uridine.

IN VIVO POLYNUCLEOTIDE DELIVERY TECHNIQUES

In additional embodiments, genetic constructs comprising one or more of the polynucleotides of the invention are introduced into cells *in vivo*. This may be achieved using any of a variety of well known approaches, several of which are outlined below for
15 the purpose of illustration.

1. ADENOVIRUS

One of the preferred methods for *in vivo* delivery of one or more nucleic acid sequences involves the use of an adenovirus expression vector. "Adenovirus expression vector" is meant to include those constructs containing adenovirus sequences
20 sufficient to (a) support packaging of the construct and (b) to express a polynucleotide that has been cloned therein in a sense or antisense orientation. Of course, in the context of an antisense construct, expression does not require that the gene product be synthesized.

The expression vector comprises a genetically engineered form of an adenovirus. Knowledge of the genetic organization of adenovirus, a 36 kb, linear, double-stranded DNA virus, allows substitution of large pieces of adenoviral DNA with foreign sequences up to 7 kb (Grunhaus and Horwitz, 1992). In contrast to retrovirus, the adenoviral infection of host cells does not result in chromosomal integration because

adenoviral DNA can replicate in an episomal manner without potential genotoxicity. Also, adenoviruses are structurally stable, and no genome rearrangement has been detected after extensive amplification. Adenovirus can infect virtually all epithelial cells regardless of their cell cycle stage. So far, adenoviral infection appears to be linked only to mild disease 5 such as acute respiratory disease in humans.

Adenovirus is particularly suitable for use as a gene transfer vector because of its mid-sized genome, ease of manipulation, high titer, wide target-cell range and high infectivity. Both ends of the viral genome contain 100-200 base pair inverted repeats (ITRs), which are *cis* elements necessary for viral DNA replication and packaging. The 10 early (E) and late (L) regions of the genome contain different transcription units that are divided by the onset of viral DNA replication. The E1 region (E1A and E1B) encodes proteins responsible for the regulation of transcription of the viral genome and a few cellular genes. The expression of the E2 region (E2A and E2B) results in the synthesis of the proteins for viral DNA replication. These proteins are involved in DNA replication, 15 late gene expression and host cell shut-off (Renan, 1990). The products of the late genes, including the majority of the viral capsid proteins, are expressed only after significant processing of a single primary transcript issued by the major late promoter (MLP). The MLP, (located at 16.8 m.u.) is particularly efficient during the late phase of infection, and all the mRNA's issued from this promoter possess a 5'-tripartite leader (TPL) sequence 20 which makes them preferred mRNA's for translation.

In a current system, recombinant adenovirus is generated from homologous recombination between shuttle vector and provirus vector. Due to the possible recombination between two proviral vectors, wild-type adenovirus may be generated from this process. Therefore, it is critical to isolate a single clone of virus from an individual 25 plaque and examine its genomic structure.

Generation and propagation of the current adenovirus vectors, which are replication deficient, depend on a unique helper cell line, designated 293, which was transformed from human embryonic kidney cells by Ad5 DNA fragments and constitutively expresses E1 proteins (Graham *et al.*, 1977). Since the E3 region is

dispensable from the adenovirus genome (Jones and Shenk, 1978), the current adenovirus vectors, with the help of 293 cells, carry foreign DNA in either the E1, the D3 or both regions (Graham and Prevec, 1991). In nature, adenovirus can package approximately 105% of the wild-type genome (Ghosh-Choudhury *et al.*, 1987), providing capacity for about 2 extra kB of DNA. Combined with the approximately 5.5 kB of DNA that is replaceable in the E1 and E3 regions, the maximum capacity of the current adenovirus vector is under 7.5 kB, or about 15% of the total length of the vector. More than 80% of the adenovirus viral genome remains in the vector backbone and is the source of vector-borne cytotoxicity. Also, the replication deficiency of the E1-deleted virus is incomplete.

For example, leakage of viral gene expression has been observed with the currently available vectors at high multiplicities of infection (MOI) (Mulligan, 1993).

Helper cell lines may be derived from human cells such as human embryonic kidney cells, muscle cells, hematopoietic cells or other human embryonic mesenchymal or epithelial cells. Alternatively, the helper cells may be derived from the cells of other mammalian species that are permissive for human adenovirus. Such cells include, *e.g.*, Vero cells or other monkey embryonic mesenchymal or epithelial cells. As stated above, the currently preferred helper cell line is 293.

Recently, Racher *et al.* (1995) disclosed improved methods for culturing 293 cells and propagating adenovirus. In one format, natural cell aggregates are grown by inoculating individual cells into 1 liter siliconized spinner flasks (Techne, Cambridge, UK) containing 100-200 ml of medium. Following stirring at 40 rpm, the cell viability is estimated with trypan blue. In another format, Fibra-Cel microcarriers (Bibby Sterlin, Stone, UK) (5 g/l) is employed as follows. A cell inoculum, resuspended in 5 ml of medium, is added to the carrier (50 ml) in a 250 ml Erlenmeyer flask and left stationary, with occasional agitation, for 1 to 4 h. The medium is then replaced with 50 ml of fresh medium and shaking initiated. For virus production, cells are allowed to grow to about 80% confluence, after which time the medium is replaced (to 25% of the final volume) and adenovirus added at an MOI of 0.05. Cultures are left stationary overnight, following which the volume is increased to 100% and shaking commenced for another 72 h.

Other than the requirement that the adenovirus vector be replication defective, or at least conditionally defective, the nature of the adenovirus vector is not believed to be crucial to the successful practice of the invention. The adenovirus may be of any of the 42 different known serotypes or subgroups A-F. Adenovirus type 5 of subgroup 5 C is the preferred starting material in order to obtain a conditional replication-defective adenovirus vector for use in the present invention, since Adenovirus type 5 is a human adenovirus about which a great deal of biochemical and genetic information is known, and it has historically been used for most constructions employing adenovirus as a vector.

As stated above, the typical vector according to the present invention is 10 replication defective and will not have an adenovirus E1 region. Thus, it will be most convenient to introduce the polynucleotide encoding the gene of interest at the position from which the E1-coding sequences have been removed. However, the position of insertion of the construct within the adenovirus sequences is not critical to the invention. The polynucleotide encoding the gene of interest may also be inserted in lieu of the deleted 15 E3 region in E3 replacement vectors as described by Karlsson *et al.* (1986) or in the E4 region where a helper cell line or helper virus complements the E4 defect.

Adenovirus is easy to grow and manipulate and exhibits broad host range *in vitro* and *in vivo*. This group of viruses can be obtained in high titers, e.g., 10^9 - 10^{11} plaque-forming units per ml, and they are highly infective. The life cycle of adenovirus does not 20 require integration into the host cell genome. The foreign genes delivered by adenovirus vectors are episomal and, therefore, have low genotoxicity to host cells. No side effects have been reported in studies of vaccination with wild-type adenovirus (Couch *et al.*, 1963; Top *et al.*, 1971), demonstrating their safety and therapeutic potential as *in vivo* gene transfer vectors.

25 Adenovirus vectors have been used in eukaryotic gene expression (Levrero *et al.*, 1991; Gomez-Foix *et al.*, 1992) and vaccine development (Grunhaus and Horwitz, 1992; Graham and Prevec, 1992). Recently, animal studies suggested that recombinant adenovirus could be used for gene therapy (Stratford-Perricaudet and Perricaudet, 1991; Stratford-Perricaudet *et al.*, 1990; Rich *et al.*, 1993). Studies in administering recombinant

adenovirus to different tissues include trachea instillation (Rosenfeld *et al.*, 1991; Rosenfeld *et al.*, 1992), muscle injection (Ragot *et al.*, 1993), peripheral intravenous injections (Herz and Gerard, 1993) and stereotactic inoculation into the brain (Le Gal La Salle *et al.*, 1993).

5 2. RETROVIRUSES

The retroviruses are a group of single-stranded RNA viruses characterized by an ability to convert their RNA to double-stranded DNA in infected cells by a process of reverse-transcription (Coffin, 1990). The resulting DNA then stably integrates into cellular chromosomes as a provirus and directs synthesis of viral proteins. The integration results 10 in the retention of the viral gene sequences in the recipient cell and its descendants. The retroviral genome contains three genes, gag, pol, and env that code for capsid proteins, polymerase enzyme, and envelope components, respectively. A sequence found upstream from the gag gene contains a signal for packaging of the genome into virions. Two long terminal repeat (LTR) sequences are present at the 5' and 3' ends of the viral genome. 15 These contain strong promoter and enhancer sequences and are also required for integration in the host cell genome (Coffin, 1990).

In order to construct a retroviral vector, a nucleic acid encoding one or more oligonucleotide or polynucleotide sequences of interest is inserted into the viral genome in the place of certain viral sequences to produce a virus that is replication-defective. In order 20 to produce virions, a packaging cell line containing the gag, pol, and env genes but without the LTR and packaging components is constructed (Mann *et al.*, 1983). When a recombinant plasmid containing a cDNA, together with the retroviral LTR and packaging sequences is introduced into this cell line (by calcium phosphate precipitation for example), the packaging sequence allows the RNA transcript of the recombinant plasmid to be 25 packaged into viral particles, which are then secreted into the culture media (Nicolas and Rubenstein, 1988; Temin, 1986; Mann *et al.*, 1983). The media containing the recombinant retroviruses is then collected, optionally concentrated, and used for gene

transfer. Retroviral vectors are able to infect a broad variety of cell types. However, integration and stable expression require the division of host cells (Paskind *et al.*, 1975).

A novel approach designed to allow specific targeting of retrovirus vectors was recently developed based on the chemical modification of a retrovirus by the chemical 5 addition of lactose residues to the viral envelope. This modification could permit the specific infection of hepatocytes *via* sialoglycoprotein receptors.

A different approach to targeting of recombinant retroviruses was designed in which biotinylated antibodies against a retroviral envelope protein and against a specific 10 cell receptor were used. The antibodies were coupled *via* the biotin components by using streptavidin (Roux *et al.*, 1989). Using antibodies against major histocompatibility complex class I and class II antigens, they demonstrated the infection of a variety of human 15 cells that bore those surface antigens with an ecotropic virus *in vitro* (Roux *et al.*, 1989).

3. ADENO-ASSOCIATED VIRUSES

AAV (Ridgeway, 1988; Hermonat and Muzycska, 1984) is a parovirus, 15 discovered as a contamination of adenoviral stocks. It is a ubiquitous virus (antibodies are present in 85% of the US human population) that has not been linked to any disease. It is also classified as a dependovirus, because its replication is dependent on the presence of a helper virus, such as adenovirus. Five serotypes have been isolated, of which AAV-2 is the best characterized. AAV has a single-stranded linear DNA that is encapsidated into capsid 20 proteins VP1, VP2 and VP3 to form an icosahedral virion of 20 to 24 nm in diameter (Muzyczka and McLaughlin, 1988).

The AAV DNA is approximately 4.7 kilobases long. It contains two open reading frames and is flanked by two ITRs. There are two major genes in the AAV genome: *rep* and *cap*. The *rep* gene codes for proteins responsible for viral replication, 25 whereas *cap* codes for capsid protein VP1-3. Each ITR forms a T-shaped hairpin structure. These terminal repeats are the only essential *cis* components of the AAV for chromosomal integration. Therefore, the AAV can be used as a vector with all viral coding sequences removed and replaced by the cassette of genes for delivery. Three viral

promoters have been identified and named p5, p19, and p40, according to their map position. Transcription from p5 and p19 results in production of rep proteins, and transcription from p40 produces the capsid proteins (Hermonat and Muzyczka, 1984).

There are several factors that prompted researchers to study the possibility
5 of using rAAV as an expression vector. One is that the requirements for delivering a gene
to integrate into the host chromosome are surprisingly few. It is necessary to have the 145-
bp ITRs, which are only 6% of the AAV genome. This leaves room in the vector to
assemble a 4.5-kb DNA insertion. While this carrying capacity may prevent the AAV from
delivering large genes, it is amply suited for delivering the antisense constructs of the
10 present invention.

AAV is also a good choice of delivery vehicles due to its safety. There is a
relatively complicated rescue mechanism: not only wild type adenovirus but also AAV
genes are required to mobilize rAAV. Likewise, AAV is not pathogenic and not associated
with any disease. The removal of viral coding sequences minimizes immune reactions to
15 viral gene expression, and therefore, rAAV does not evoke an inflammatory response.

4. OTHER VIRAL VECTORS AS EXPRESSION CONSTRUCTS

Other viral vectors may be employed as expression constructs in the present
invention for the delivery of oligonucleotide or polynucleotide sequences to a host cell.
Vectors derived from viruses such as vaccinia virus (Ridgeway, 1988; Coupar *et al.*, 1988),
20 lentiviruses, polio viruses and herpes viruses may be employed. They offer several
attractive features for various mammalian cells (Friedmann, 1989; Ridgeway, 1988;
Coupar *et al.*, 1988; Horwich *et al.*, 1990).

With the recent recognition of defective hepatitis B viruses, new insight was
gained into the structure-function relationship of different viral sequences. *In vitro* studies
25 showed that the virus could retain the ability for helper-dependent packaging and reverse
transcription despite the deletion of up to 80% of its genome (Horwich *et al.*, 1990). This
suggested that large portions of the genome could be replaced with foreign genetic
material. The hepatotropism and persistence (integration) were particularly attractive

properties for liver-directed gene transfer. Chang *et al.* (1991) introduced the chloramphenicol acetyltransferase (CAT) gene into duck hepatitis B virus genome in the place of the polymerase, surface, and pre-surface coding sequences. It was cotransfected with wild-type virus into an avian hepatoma cell line. Culture media containing high titers 5 of the recombinant virus were used to infect primary duckling hepatocytes. Stable CAT gene expression was detected for at least 24 days after transfection (Chang *et al.*, 1991).

5. NON-VIRAL VECTORS

In order to effect expression of the oligonucleotide or polynucleotide sequences of the present invention, the expression construct must be delivered into a cell. 10 This delivery may be accomplished *in vitro*, as in laboratory procedures for transforming cells lines, or *in vivo* or *ex vivo*, as in the treatment of certain disease states. As described above, one preferred mechanism for delivery is *via* viral infection where the expression construct is encapsulated in an infectious viral particle.

Once the expression construct has been delivered into the cell the nucleic 15 acid encoding the desired oligonucleotide or polynucleotide sequences may be positioned and expressed at different sites. In certain embodiments, the nucleic acid encoding the construct may be stably integrated into the genome of the cell. This integration may be in the specific location and orientation *via* homologous recombination (gene replacement) or it may be integrated in a random, non-specific location (gene augmentation). In yet further 20 embodiments, the nucleic acid may be stably maintained in the cell as a separate, episomal segment of DNA. Such nucleic acid segments or "episomes" encode sequences sufficient to permit maintenance and replication independent of or in synchronization with the host cell cycle. How the expression construct is delivered to a cell and where in the cell the nucleic acid remains is dependent on the type of expression construct employed.

25 In certain embodiments of the invention, the expression construct comprising one or more oligonucleotide or polynucleotide sequences may simply consist of naked recombinant DNA or plasmids. Transfer of the construct may be performed by any of the methods mentioned above which physically or chemically permeabilize the cell

membrane. This is particularly applicable for transfer *in vitro* but it may be applied to *in vivo* use as well. Dubensky *et al.* (1984) successfully injected polyomavirus DNA in the form of calcium phosphate precipitates into liver and spleen of adult and newborn mice demonstrating active viral replication and acute infection. Benvenisty and Reshef (1986) 5 also demonstrated that direct intraperitoneal injection of calcium phosphate-precipitated plasmids results in expression of the transfected genes. It is envisioned that DNA encoding a gene of interest may also be transferred in a similar manner *in vivo* and express the gene product.

Another embodiment of the invention for transferring a naked DNA 10 expression construct into cells may involve particle bombardment. This method depends on the ability to accelerate DNA-coated microprojectiles to a high velocity allowing them to pierce cell membranes and enter cells without killing them (Klein *et al.*, 1987). Several devices for accelerating small particles have been developed. One such device relies on a high voltage discharge to generate an electrical current, which in turn provides the motive 15 force (Yang *et al.*, 1990). The microprojectiles used have consisted of biologically inert substances such as tungsten or gold beads.

Selected organs including the liver, skin, and muscle tissue of rats and mice 20 have been bombarded *in vivo* (Yang *et al.*, 1990; Zelenin *et al.*, 1991). This may require surgical exposure of the tissue or cells, to eliminate any intervening tissue between the gun and the target organ, *i.e. ex vivo* treatment. Again, DNA encoding a particular gene may be delivered *via* this method and still be incorporated by the present invention.

ANTISENSE OLIGONUCLEOTIDES

The end result of the flow of genetic information is the synthesis of protein. DNA is transcribed by polymerases into messenger RNA and translated on the ribosome to 25 yield a folded, functional protein. Thus there are several steps along the route where protein synthesis can be inhibited. The native DNA segment coding for a polypeptide described herein, as all such mammalian DNA strands, has two strands: a sense strand and an antisense strand held together by hydrogen bonding. The messenger RNA coding for

polypeptide has the same nucleotide sequence as the sense DNA strand except that the DNA thymidine is replaced by uridine. Thus, synthetic antisense nucleotide sequences will bind to a mRNA and inhibit expression of the protein encoded by that mRNA.

The targeting of antisense oligonucleotides to mRNA is thus one mechanism
5 to shut down protein synthesis, and, consequently, represents a powerful and targeted therapeutic approach. For example, the synthesis of polygalacturonase and the muscarine type 2 acetylcholine receptor are inhibited by antisense oligonucleotides directed to their respective mRNA sequences (U. S. Patent 5,739,119 and U. S. Patent 5,759,829, each specifically incorporated herein by reference in its entirety). Further, examples of antisense
10 inhibition have been demonstrated with the nuclear protein cyclin, the multiple drug resistance gene (MDG1), ICAM-1, E-selectin, STK-1, striatal GABA_A receptor and human EGF (Jaskulski *et al.*, 1988; Vasantha Kumar and Ahmed, 1989; Peris *et al.*, 1998; U. S. Patent 5,801,154; U. S. Patent 5,789,573; U. S. Patent 5,718,709 and U. S. Patent 5,610,288, each specifically incorporated herein by reference in its entirety). Antisense
15 constructs have also been described that inhibit and can be used to treat a variety of abnormal cellular proliferations, *e.g.* cancer (U. S. Patent 5,747,470; U. S. Patent 5,591,317 and U. S. Patent 5,783,683, each specifically incorporated herein by reference in its entirety).

Therefore, in exemplary embodiments, the invention provides
20 oligonucleotide sequences that comprise all, or a portion of, any sequence that is capable of specifically binding to polynucleotide sequence described herein, or a complement thereof. In one embodiment, the antisense oligonucleotides comprise DNA or derivatives thereof. In another embodiment, the oligonucleotides comprise RNA or derivatives thereof. In a third embodiment, the oligonucleotides are modified DNAs comprising a
25 phosphorothioated modified backbone. In a fourth embodiment, the oligonucleotide sequences comprise peptide nucleic acids or derivatives thereof. In each case, preferred compositions comprise a sequence region that is complementary, and more preferably substantially-complementary, and even more preferably, completely complementary to one or more portions of polynucleotides disclosed herein.

Selection of antisense compositions specific for a given gene sequence is based upon analysis of the chosen target sequence (*i.e.* in these illustrative examples the rat and human sequences) and determination of secondary structure, T_m , binding energy, relative stability, and antisense compositions were selected based upon their relative 5 inability to form dimers, hairpins, or other secondary structures that would reduce or prohibit specific binding to the target mRNA in a host cell.

Highly preferred target regions of the mRNA, are those which are at or near the AUG translation initiation codon, and those sequences which were substantially complementary to 5' regions of the mRNA. These secondary structure analyses and target 10 site selection considerations were performed using v.4 of the OLIGO primer analysis software (Rychlik, 1997) and the BLASTN 2.0.5 algorithm software (Altschul *et al.*, 1997).

The use of an antisense delivery method employing a short peptide vector, termed MPG (27 residues), is also contemplated. The MPG peptide contains a hydrophobic domain derived from the fusion sequence of HIV gp41 and a hydrophilic 15 domain from the nuclear localization sequence of SV40 T-antigen (Morris *et al.*, 1997). It has been demonstrated that several molecules of the MPG peptide coat the antisense oligonucleotides and can be delivered into cultured mammalian cells in less than 1 hour with relatively high efficiency (90%). Further, the interaction with MPG strongly increases both the stability of the oligonucleotide to nuclease and the ability to cross the plasma 20 membrane (Morris *et al.*, 1997).

RIBOZYMES

Although proteins traditionally have been used for catalysis of nucleic acids, another class of macromolecules has emerged as useful in this endeavor. Ribozymes are RNA-protein complexes that cleave nucleic acids in a site-specific fashion. Ribozymes 25 have specific catalytic domains that possess endonuclease activity (Kim and Cech, 1987; Gerlach *et al.*, 1987; Forster and Symons, 1987). For example, a large number of ribozymes accelerate phosphoester transfer reactions with a high degree of specificity, often cleaving only one of several phosphoesters in an oligonucleotide substrate (Cech *et*

al., 1981; Michel and Westhof, 1990; Reinhold-Hurek and Shub, 1992). This specificity has been attributed to the requirement that the substrate bind via specific base-pairing interactions to the internal guide sequence ("IGS") of the ribozyme prior to chemical reaction.

5 Ribozyme catalysis has primarily been observed as part of sequence-specific cleavage/ligation reactions involving nucleic acids (Joyce, 1989; Cech *et al.*, 1981). For example, U. S. Patent No. 5,354,855 (specifically incorporated herein by reference) reports that certain ribozymes can act as endonucleases with a sequence specificity greater than that of known ribonucleases and approaching that of the DNA restriction enzymes. Thus,
10 sequence-specific ribozyme-mediated inhibition of gene expression may be particularly suited to therapeutic applications (Scanlon *et al.*, 1991; Sarver *et al.*, 1990). Recently, it was reported that ribozymes elicited genetic changes in some cell lines to which they were applied; the altered genes included the oncogenes H-ras, c-fos and genes of HIV. Most of this work involved the modification of a target mRNA, based on a specific mutant codon
15 that is cleaved by a specific ribozyme.

6 Six basic varieties of naturally-occurring enzymatic RNAs are known presently. Each can catalyze the hydrolysis of RNA phosphodiester bonds *in trans* (and thus can cleave other RNA molecules) under physiological conditions. In general, enzymatic nucleic acids act by first binding to a target RNA. Such binding occurs through
20 the target binding portion of a enzymatic nucleic acid which is held in close proximity to an enzymatic portion of the molecule that acts to cleave the target RNA. Thus, the enzymatic nucleic acid first recognizes and then binds a target RNA through complementary base-pairing, and once bound to the correct site, acts enzymatically to cut the target RNA. Strategic cleavage of such a target RNA will destroy its ability to direct synthesis of an
25 encoded protein. After an enzymatic nucleic acid has bound and cleaved its RNA target, it is released from that RNA to search for another target and can repeatedly bind and cleave new targets.

7 The enzymatic nature of a ribozyme is advantageous over many technologies, such as antisense technology (where a nucleic acid molecule simply binds to

a nucleic acid target to block its translation) since the concentration of ribozyme necessary to affect a therapeutic treatment is lower than that of an antisense oligonucleotide. This advantage reflects the ability of the ribozyme to act enzymatically. Thus, a single ribozyme molecule is able to cleave many molecules of target RNA. In addition, the 5 ribozyme is a highly specific inhibitor, with the specificity of inhibition depending not only on the base pairing mechanism of binding to the target RNA, but also on the mechanism of target RNA cleavage. Single mismatches, or base-substitutions, near the site of cleavage can completely eliminate catalytic activity of a ribozyme. Similar mismatches in antisense molecules do not prevent their action (Woolf *et al.*, 1992). Thus, the specificity of action 10 of a ribozyme is greater than that of an antisense oligonucleotide binding the same RNA site.

The enzymatic nucleic acid molecule may be formed in a hammerhead, hairpin, a hepatitis δ virus, group I intron or RNaseP RNA (in association with an RNA guide sequence) or Neurospora VS RNA motif. Examples of hammerhead motifs are 15 described by Rossi *et al.* (1992). Examples of hairpin motifs are described by Hampel *et al.* (Eur. Pat. Appl. Publ. No. EP 0360257), Hampel and Tritz (1989), Hampel *et al.* (1990) and U. S. Patent 5,631,359 (specifically incorporated herein by reference). An example of the hepatitis δ virus motif is described by Perrotta and Been (1992); an example 20 of the RNaseP motif is described by Guerrier-Takada *et al.* (1983); Neurospora VS RNA ribozyme motif is described by Collins (Saville and Collins, 1990; Saville and Collins, 1991; Collins and Olive, 1993); and an example of the Group I intron is described in (U. S. Patent 4,987,071, specifically incorporated herein by reference). All that is important in an 25 enzymatic nucleic acid molecule of this invention is that it has a specific substrate binding site which is complementary to one or more of the target gene RNA regions, and that it have nucleotide sequences within or surrounding that substrate binding site which impart an RNA cleaving activity to the molecule. Thus the ribozyme constructs need not be limited to specific motifs mentioned herein.

In certain embodiments, it may be important to produce enzymatic cleaving agents which exhibit a high degree of specificity for the RNA of a desired target, such as

one of the sequences disclosed herein. The enzymatic nucleic acid molecule is preferably targeted to a highly conserved sequence region of a target mRNA. Such enzymatic nucleic acid molecules can be delivered exogenously to specific cells as required. Alternatively, the ribozymes can be expressed from DNA or RNA vectors that are delivered to specific
5 cells.

Small enzymatic nucleic acid motifs (*e.g.*, of the hammerhead or the hairpin structure) may also be used for exogenous delivery. The simple structure of these molecules increases the ability of the enzymatic nucleic acid to invade targeted regions of the mRNA structure. Alternatively, catalytic RNA molecules can be expressed within cells
10 from eukaryotic promoters (*e.g.*, Scanlon *et al.*, 1991; Kashani-Sabet *et al.*, 1992; Dropulic *et al.*, 1992; Weerasinghe *et al.*, 1991; Ojwang *et al.*, 1992; Chen *et al.*, 1992; Sarver *et al.*, 1990). Those skilled in the art realize that any ribozyme can be expressed in eukaryotic cells from the appropriate DNA vector. The activity of such ribozymes can be augmented by their release from the primary transcript by a second ribozyme (Int. Pat. Appl. Publ. No.
15 WO 93/23569, and Int. Pat. Appl. Publ. No. WO 94/02595, both hereby incorporated by reference; Ohkawa *et al.*, 1992; Taira *et al.*, 1991; and Ventura *et al.*, 1993).

Ribozymes may be added directly, or can be complexed with cationic lipids, lipid complexes, packaged within liposomes, or otherwise delivered to target cells. The RNA or RNA complexes can be locally administered to relevant tissues *ex vivo*, or *in vivo*
20 through injection, aerosol inhalation, infusion pump or stent, with or without their incorporation in biopolymers.

Ribozymes may be designed as described in Int. Pat. Appl. Publ. No. WO 93/23569 and Int. Pat. Appl. Publ. No. WO 94/02595, each specifically incorporated herein by reference) and synthesized to be tested *in vitro* and *in vivo*, as described. Such
25 ribozymes can also be optimized for delivery. While specific examples are provided, those in the art will recognize that equivalent RNA targets in other species can be utilized when necessary.

Hammerhead or hairpin ribozymes may be individually analyzed by computer folding (Jaeger *et al.*, 1989) to assess whether the ribozyme sequences fold into

the appropriate secondary structure. Those ribozymes with unfavorable intramolecular interactions between the binding arms and the catalytic core are eliminated from consideration. Varying binding arm lengths can be chosen to optimize activity. Generally, at least 5 or so bases on each arm are able to bind to, or otherwise interact with, the target 5 RNA.

Ribozymes of the hammerhead or hairpin motif may be designed to anneal to various sites in the mRNA message, and can be chemically synthesized. The method of synthesis used follows the procedure for normal RNA synthesis as described in Usman *et al.* (1987) and in Scaringe *et al.* (1990) and makes use of common nucleic acid 10 protecting and coupling groups, such as dimethoxytrityl at the 5'-end, and phosphoramidites at the 3'-end. Average stepwise coupling yields are typically >98%. Hairpin ribozymes may be synthesized in two parts and annealed to reconstruct an active 15 ribozyme (Chowrima and Burke, 1992). Ribozymes may be modified extensively to enhance stability by modification with nuclease resistant groups, for example, 2'-amino, 2'-C-allyl, 2'-flouro, 2'-o-methyl, 2'-H (for a review see e.g., Usman and Cedergren, 1992). Ribozymes may be purified by gel electrophoresis using general methods or by high pressure liquid chromatography and resuspended in water.

Ribozyme activity can be optimized by altering the length of the ribozyme binding arms, or chemically synthesizing ribozymes with modifications that prevent their 20 degradation by serum ribonucleases (see e.g., Int. Pat. Appl. Publ. No. WO 92/07065; Perrault *et al.*, 1990; Pieken *et al.*, 1991; Usman and Cedergren, 1992; Int. Pat. Appl. Publ. No. WO 93/15187; Int. Pat. Appl. Publ. No. WO 91/03162; Eur. Pat. Appl. Publ. No. 92110298.4; U. S. Patent 5,334,711; and Int. Pat. Appl. Publ. No. WO 94/13688, which describe various chemical modifications that can be made to the sugar moieties of 25 enzymatic RNA molecules), modifications which enhance their efficacy in cells, and removal of stem II bases to shorten RNA synthesis times and reduce chemical requirements.

Sullivan *et al.* (Int. Pat. Appl. Publ. No. WO 94/02595) describes the general methods for delivery of enzymatic RNA molecules. Ribozymes may be

administered to cells by a variety of methods known to those familiar to the art, including, but not restricted to, encapsulation in liposomes, by iontophoresis, or by incorporation into other vehicles, such as hydrogels, cyclodextrins, biodegradable nanocapsules, and bioadhesive microspheres. For some indications, ribozymes may be directly delivered *ex vivo* to cells or tissues with or without the aforementioned vehicles. Alternatively, the RNA/vehicle combination may be locally delivered by direct inhalation, by direct injection or by use of a catheter, infusion pump or stent. Other routes of delivery include, but are not limited to, intravascular, intramuscular, subcutaneous or joint injection, aerosol inhalation, oral (tablet or pill form), topical, systemic, ocular, intraperitoneal and/or intrathecal delivery. More detailed descriptions of ribozyme delivery and administration are provided in Int. Pat. Appl. Publ. No. WO 94/02595 and Int. Pat. Appl. Publ. No. WO 93/23569, each specifically incorporated herein by reference.

Another means of accumulating high concentrations of a ribozyme(s) within cells is to incorporate the ribozyme-encoding sequences into a DNA expression vector. Transcription of the ribozyme sequences are driven from a promoter for eukaryotic RNA polymerase I (pol I), RNA polymerase II (pol II), or RNA polymerase III (pol III). Transcripts from pol II or pol III promoters will be expressed at high levels in all cells; the levels of a given pol II promoter in a given cell type will depend on the nature of the gene regulatory sequences (enhancers, silencers, *etc.*) present nearby. Prokaryotic RNA polymerase promoters may also be used, providing that the prokaryotic RNA polymerase enzyme is expressed in the appropriate cells (Elroy-Stein and Moss, 1990; Gao and Huang, 1993; Lieber *et al.*, 1993; Zhou *et al.*, 1990). Ribozymes expressed from such promoters can function in mammalian cells (*e.g.* Kashani-Saber *et al.*, 1992; Ojwang *et al.*, 1992; Chen *et al.*, 1992; Yu *et al.*, 1993; L'Huillier *et al.*, 1992; Lisziewicz *et al.*, 1993). Such transcription units can be incorporated into a variety of vectors for introduction into mammalian cells, including but not restricted to, plasmid DNA vectors, viral DNA vectors (such as adenovirus or adeno-associated vectors), or viral RNA vectors (such as retroviral, semliki forest virus, sindbis virus vectors).

Ribozymes may be used as diagnostic tools to examine genetic drift and mutations within diseased cells. They can also be used to assess levels of the target RNA molecule. The close relationship between ribozyme activity and the structure of the target RNA allows the detection of mutations in any region of the molecule which alters the base-pairing and three-dimensional structure of the target RNA. By using multiple ribozymes, one may map nucleotide changes which are important to RNA structure and function *in vitro*, as well as in cells and tissues. Cleavage of target RNAs with ribozymes may be used to inhibit gene expression and define the role (essentially) of specified gene products in the progression of disease. In this manner, other genetic targets may be defined as important mediators of the disease. These studies will lead to better treatment of the disease progression by affording the possibility of combinational therapies (*e.g.*, multiple ribozymes targeted to different genes, ribozymes coupled with known small molecule inhibitors, or intermittent treatment with combinations of ribozymes and/or other chemical or biological molecules). Other *in vitro* uses of ribozymes are well known in the art, and include detection of the presence of mRNA associated with an IL-5 related condition. Such RNA is detected by determining the presence of a cleavage product after treatment with a ribozyme using standard methodology.

PEPTIDE NUCLEIC ACIDS

In certain embodiments, the inventors contemplate the use of peptide nucleic acids (PNAs) in the practice of the methods of the invention. PNA is a DNA mimic in which the nucleobases are attached to a pseudopeptide backbone (Good and Nielsen, 1997). PNA is able to be utilized in a number methods that traditionally have used RNA or DNA. Often PNA sequences perform better in techniques than the corresponding RNA or DNA sequences and have utilities that are not inherent to RNA or DNA. A review of PNA including methods of making, characteristics of, and methods of using, is provided by Corey (1997) and is incorporated herein by reference. As such, in certain embodiments, one may prepare PNA sequences that are complementary to one or more portions of the ACE mRNA sequence, and such PNA compositions may be used to regulate, alter,

decrease, or reduce the translation of ACE-specific mRNA, and thereby alter the level of ACE activity in a host cell to which such PNA compositions have been administered.

PNAs have 2-aminoethyl-glycine linkages replacing the normal phosphodiester backbone of DNA (Nielsen *et al.*, 1991; Hanvey *et al.*, 1992; Hyrup and Nielsen, 1996; Nielsen, 1996). This chemistry has three important consequences: firstly, in contrast to DNA or phosphorothioate oligonucleotides, PNAs are neutral molecules; secondly, PNAs are achiral, which avoids the need to develop a stereoselective synthesis; and thirdly, PNA synthesis uses standard Boc (Dueholm *et al.*, 1994) or Fmoc (Thomson *et al.*, 1995) protocols for solid-phase peptide synthesis, although other methods, including a modified Merrifield method, have been used (Christensen *et al.*, 1995).

PNA monomers or ready-made oligomers are commercially available from PerSeptive Biosystems (Framingham, MA). PNA syntheses by either Boc or Fmoc protocols are straightforward using manual or automated protocols (Norton *et al.*, 1995). The manual protocol lends itself to the production of chemically modified PNAs or the simultaneous synthesis of families of closely related PNAs.

As with peptide synthesis, the success of a particular PNA synthesis will depend on the properties of the chosen sequence. For example, while in theory PNAs can incorporate any combination of nucleotide bases, the presence of adjacent purines can lead to deletions of one or more residues in the product. In expectation of this difficulty, it is suggested that, in producing PNAs with adjacent purines, one should repeat the coupling of residues likely to be added inefficiently. This should be followed by the purification of PNAs by reverse-phase high-pressure liquid chromatography (Norton *et al.*, 1995) providing yields and purity of product similar to those observed during the synthesis of peptides.

Modifications of PNAs for a given application may be accomplished by coupling amino acids during solid-phase synthesis or by attaching compounds that contain a carboxylic acid group to the exposed N-terminal amine. Alternatively, PNAs can be modified after synthesis by coupling to an introduced lysine or cysteine. The ease with which PNAs can be modified facilitates optimization for better solubility or for specific

functional requirements. Once synthesized, the identity of PNAs and their derivatives can be confirmed by mass spectrometry. Several studies have made and utilized modifications of PNAs (Norton *et al.*, 1995; Haaima *et al.*, 1996; Stetsenko *et al.*, 1996; Petersen *et al.*, 1995; Ulmann *et al.*, 1996; Koch *et al.*, 1995; Orum *et al.*, 1995; Footer *et al.*, 1996; 5 Griffith *et al.*, 1995; Kremsky *et al.*, 1996; Pardridge *et al.*, 1995; Boffa *et al.*, 1995; Landsdorp *et al.*, 1996; Gambacorti-Passerini *et al.*, 1996; Armitage *et al.*, 1997; Seeger *et al.*, 1997; Ruskowski *et al.*, 1997). U.S. Patent No. 5,700,922 discusses PNA-DNA-PNA chimeric molecules and their uses in diagnostics, modulating protein in organisms, and treatment of conditions susceptible to therapeutics.

10 In contrast to DNA and RNA, which contain negatively charged linkages, the PNA backbone is neutral. In spite of this dramatic alteration, PNAs recognize complementary DNA and RNA by Watson-Crick pairing (Egholm *et al.*, 1993), validating the initial modeling by Nielsen *et al.* (1991). PNAs lack 3' to 5' polarity and can bind in either parallel or antiparallel fashion, with the antiparallel mode being preferred (Egholm *et al.*, 1993).

15 Hybridization of DNA oligonucleotides to DNA and RNA is destabilized by electrostatic repulsion between the negatively charged phosphate backbones of the complementary strands. By contrast, the absence of charge repulsion in PNA-DNA or PNA-RNA duplexes increases the melting temperature (T_m) and reduces the dependence of 20 T_m on the concentration of mono- or divalent cations (Nielsen *et al.*, 1991). The enhanced rate and affinity of hybridization are significant because they are responsible for the surprising ability of PNAs to perform strand invasion of complementary sequences within relaxed double-stranded DNA. In addition, the efficient hybridization at inverted repeats suggests that PNAs can recognize secondary structure effectively within double-stranded 25 DNA. Enhanced recognition also occurs with PNAs immobilized on surfaces, and Wang *et al.* have shown that support-bound PNAs can be used to detect hybridization events (Wang *et al.*, 1996).

One might expect that tight binding of PNAs to complementary sequences would also increase binding to similar (but not identical) sequences, reducing the sequence

specificity of PNA recognition. As with DNA hybridization, however, selective recognition can be achieved by balancing oligomer length and incubation temperature. Moreover, selective hybridization of PNAs is encouraged by PNA-DNA hybridization being less tolerant of base mismatches than DNA-DNA hybridization. For example, a 5 single mismatch within a 16 bp PNA-DNA duplex can reduce the T_m by up to 15°C (Egholm *et al.*, 1993). This high level of discrimination has allowed the development of several PNA-based strategies for the analysis of point mutations (Wang *et al.*, 1996; Carlsson *et al.*, 1996; Thiede *et al.*, 1996; Webb and Hurskainen, 1996; Perry-O'Keefe *et al.*, 1996).

10 High-affinity binding provides clear advantages for molecular recognition and the development of new applications for PNAs. For example, 11-13 nucleotide PNAs inhibit the activity of telomerase, a ribonucleo-protein that extends telomere ends using an essential RNA template, while the analogous DNA oligomers do not (Norton *et al.*, 1996).

15 Neutral PNAs are more hydrophobic than analogous DNA oligomers, and this can lead to difficulty solubilizing them at neutral pH, especially if the PNAs have a high purine content or if they have the potential to form secondary structures. Their solubility can be enhanced by attaching one or more positive charges to the PNA termini (Nielsen *et al.*, 1991).

20 Findings by Allfrey and colleagues suggest that strand invasion will occur spontaneously at sequences within chromosomal DNA (Boffa *et al.*, 1995; Boffa *et al.*, 1996). These studies targeted PNAs to triplet repeats of the nucleotides CAG and used this recognition to purify transcriptionally active DNA (Boffa *et al.*, 1995) and to inhibit transcription (Boffa *et al.*, 1996). This result suggests that if PNAs can be delivered within cells then they will have the potential to be general sequence-specific regulators of gene expression. Studies and reviews concerning the use of PNAs as antisense and anti-gene agents include Nielsen *et al.* (1993b), Hanvey *et al.* (1992), and Good and Nielsen (1997). Koppelhus *et al.* (1997) have used PNAs to inhibit HIV-1 inverse transcription, showing that PNAs may be used for antiviral therapies.

Methods of characterizing the antisense binding properties of PNAs are discussed in Rose (1993) and Jensen *et al.* (1997). Rose uses capillary gel electrophoresis to determine binding of PNAs to their complementary oligonucleotide, measuring the relative binding kinetics and stoichiometry. Similar types of measurements were made by 5 Jensen *et al.* using BIACore™ technology.

Other applications of PNAs include use in DNA strand invasion (Nielsen *et al.*, 1991), antisense inhibition (Hanvey *et al.*, 1992), mutational analysis (Orum *et al.*, 1993), enhancers of transcription (Mollegaard *et al.*, 1994), nucleic acid purification (Orum *et al.*, 1995), isolation of transcriptionally active genes (Boffa *et al.*, 1995), blocking of 10 transcription factor binding (Vickers *et al.*, 1995), genome cleavage (Veselkov *et al.*, 1996), biosensors (Wang *et al.*, 1996), *in situ* hybridization (Thisted *et al.*, 1996), and in a alternative to Southern blotting (Perry-O'Keefe, 1996).

POLYPEPTIDE COMPOSITIONS

The present invention, in other aspects, provides polypeptide compositions. 15 Generally, a polypeptide of the invention will be an isolated polypeptide (or an epitope, variant, or active fragment thereof) derived from a mammalian species. Preferably, the polypeptide is encoded by a polynucleotide sequence disclosed herein or a sequence which hybridizes under moderately stringent conditions to a polynucleotide sequence disclosed herein. Alternatively, the polypeptide may be defined as a polypeptide which comprises a 20 contiguous amino acid sequence from an amino acid sequence disclosed herein, or which polypeptide comprises an entire amino acid sequence disclosed herein.

In the present invention, a polypeptide composition is also understood to comprise one or more polypeptides that are immunologically reactive with antibodies generated against a polypeptide of the invention, particularly a polypeptide having the 25 amino acid sequence disclosed in SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380, 383, 477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568, 573-586, 588-590, 592, 706-708, 775, 776, 778 and 780, or active fragments, variants or biological functional equivalents thereof.

Likewise, a polypeptide composition of the present invention is understood to comprise one or more polypeptides that are capable of eliciting antibodies that are immunologically reactive with one or more polypeptides encoded by one or more contiguous nucleic acid sequences contained in SEQ ID NO: 1-111, 115-171, 173-175, 5 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777 and 789, or to active fragments, or to variants thereof, or to one or more nucleic acid sequences which hybridize to one or more of these sequences under conditions of moderate to high stringency. Particularly illustrative polypeptides include the amino acid sequence disclosed 10 in SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380, 383, 477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568, 573-586, 588-590, 592, 706-708, 775, 776, 778 and 780.

As used herein, an active fragment of a polypeptide includes a whole or a portion of a polypeptide which is modified by conventional techniques, *e.g.*, mutagenesis, 15 or by addition, deletion, or substitution, but which active fragment exhibits substantially the same structure function, antigenicity, etc., as a polypeptide as described herein.

In certain illustrative embodiments, the polypeptides of the invention will comprise at least an immunogenic portion of a prostate-specific protein or a variant thereof, as described herein. As noted above, a "prostate-specific protein" is a protein that is 20 expressed by prostate cells. Proteins that are prostate-specific proteins also react detectably within an immunoassay (such as an ELISA) with antisera from a patient with prostate cancer. Polypeptides as described herein may be of any length. Additional sequences derived from the native protein and/or heterologous sequences may be present, and such sequences may (but need not) possess further immunogenic or antigenic properties.

25 An "immunogenic portion," as used herein is a portion of a protein that is recognized (*i.e.*, specifically bound) by a B-cell and/or T-cell surface antigen receptor. Such immunogenic portions generally comprise at least 5 amino acid residues, more preferably at least 10, and still more preferably at least 20 amino acid residues of a prostate-specific protein or a variant thereof. Certain preferred immunogenic portions

include peptides in which an N-terminal leader sequence and/or transmembrane domain have been deleted. Other preferred immunogenic portions may contain a small N- and/or C-terminal deletion (*e.g.*, 1-30 amino acids, preferably 5-15 amino acids), relative to the mature protein.

5 Immunogenic portions may generally be identified using well known techniques, such as those summarized in Paul, *Fundamental Immunology*, 3rd ed., 243-247 (Raven Press, 1993) and references cited therein. Such techniques include screening polypeptides for the ability to react with antigen-specific antibodies, antisera and/or T-cell lines or clones. As used herein, antisera and antibodies are "antigen-specific" if they
10 specifically bind to an antigen (*i.e.*, they react with the protein in an ELISA or other immunoassay, and do not react detectably with unrelated proteins). Such antisera and antibodies may be prepared as described herein, and using well known techniques. An immunogenic portion of a native prostate-specific protein is a portion that reacts with such antisera and/or T-cells at a level that is not substantially less than the reactivity of the full
15 length polypeptide (*e.g.*, in an ELISA and/or T-cell reactivity assay). Such immunogenic portions may react within such assays at a level that is similar to or greater than the reactivity of the full length polypeptide. Such screens may generally be performed using methods well known to those of ordinary skill in the art, such as those described in Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. For
20 example, a polypeptide may be immobilized on a solid support and contacted with patient sera to allow binding of antibodies within the sera to the immobilized polypeptide. Unbound sera may then be removed and bound antibodies detected using, for example,
¹²⁵I-labeled Protein A.

As noted above, a composition may comprise a variant of a native prostate-
25 specific protein. A polypeptide "variant," as used herein, is a polypeptide that differs from a native prostate-specific protein in one or more substitutions, deletions, additions and/or insertions, such that the immunogenicity of the polypeptide is not substantially diminished. In other words, the ability of a variant to react with antigen-specific antisera may be enhanced or unchanged, relative to the native protein, or may be diminished by less than

50%, and preferably less than 20%, relative to the native protein. Such variants may generally be identified by modifying one of the above polypeptide sequences and evaluating the reactivity of the modified polypeptide with antigen-specific antibodies or antisera as described herein. Preferred variants include those in which one or more portions, such as an N-terminal leader sequence or transmembrane domain, have been removed. Other preferred variants include variants in which a small portion (*e.g.*, 1-30 amino acids, preferably 5-15 amino acids) has been removed from the N- and/or C-terminal of the mature protein.

Polypeptide variants encompassed by the present invention include those exhibiting at least about 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% or more identity (determined as described above) to the polypeptides disclosed herein.

Preferably, a variant contains conservative substitutions. A "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydropathic nature of the polypeptide to be substantially unchanged. Amino acid substitutions may generally be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the residues. For example, negatively charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include lysine and arginine; and amino acids with uncharged polar head groups having similar hydrophilicity values include leucine, isoleucine and valine; glycine and alanine; asparagine and glutamine; and serine, threonine, phenylalanine and tyrosine. Other groups of amino acids that may represent conservative changes include: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his. A variant may also, or alternatively, contain nonconservative changes. In a preferred embodiment, variant polypeptides differ from a native sequence by substitution, deletion or addition of five amino acids or fewer. Variants may also (or alternatively) be modified by, for example, the

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deletion or addition of amino acids that have minimal influence on the immunogenicity, secondary structure and hydropathic nature of the polypeptide.

As noted above, polypeptides may comprise a signal (or leader) sequence at the N-terminal end of the protein, which co-translationally or post-translationally directs transfer of the protein. The polypeptide may also be conjugated to a linker or other sequence for ease of synthesis, purification or identification of the polypeptide (e.g., poly-His), or to enhance binding of the polypeptide to a solid support. For example, a polypeptide may be conjugated to an immunoglobulin Fc region.

Polypeptides may be prepared using any of a variety of well known techniques. Recombinant polypeptides encoded by DNA sequences as described above may be readily prepared from the DNA sequences using any of a variety of expression vectors known to those of ordinary skill in the art. Expression may be achieved in any appropriate host cell that has been transformed or transfected with an expression vector containing a DNA molecule that encodes a recombinant polypeptide. Suitable host cells include prokaryotes, yeast, and higher eukaryotic cells, such as mammalian cells and plant cells. Preferably, the host cells employed are *E. coli*, yeast or a mammalian cell line such as COS or CHO. Supernatants from suitable host/vector systems which secrete recombinant protein or polypeptide into culture media may be first concentrated using a commercially available filter. Following concentration, the concentrate may be applied to a suitable purification matrix such as an affinity matrix or an ion exchange resin. Finally, one or more reverse phase HPLC steps can be employed to further purify a recombinant polypeptide.

Portions and other variants having less than about 100 amino acids, and generally less than about 50 amino acids, may also be generated by synthetic means, using techniques well known to those of ordinary skill in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain. *See* Merrifield, *J. Am. Chem. Soc.* 85:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from

suppliers such as Perkin Elmer/Applied BioSystems Division (Foster City, CA), and may be operated according to the manufacturer's instructions.

Within certain specific embodiments, a polypeptide may be a fusion protein that comprises multiple polypeptides as described herein, or that comprises at least one polypeptide as described herein and an unrelated sequence, such as a known tumor protein. A fusion partner may, for example, assist in providing T helper epitopes (an immunological fusion partner), preferably T helper epitopes recognized by humans, or may assist in expressing the protein (an expression enhancer) at higher yields than the native recombinant protein. Certain preferred fusion partners are both immunological and expression enhancing fusion partners. Other fusion partners may be selected so as to increase the solubility of the protein or to enable the protein to be targeted to desired intracellular compartments. Still further fusion partners include affinity tags, which facilitate purification of the protein.

Fusion proteins may generally be prepared using standard techniques, including chemical conjugation. Preferably, a fusion protein is expressed as a recombinant protein, allowing the production of increased levels, relative to a non-fused protein, in an expression system. Briefly, DNA sequences encoding the polypeptide components may be assembled separately, and ligated into an appropriate expression vector. The 3' end of the DNA sequence encoding one polypeptide component is ligated, with or without a peptide linker, to the 5' end of a DNA sequence encoding the second polypeptide component so that the reading frames of the sequences are in phase. This permits translation into a single fusion protein that retains the biological activity of both component polypeptides.

A peptide linker sequence may be employed to separate the first and second polypeptide components by a distance sufficient to ensure that each polypeptide folds into its secondary and tertiary structures. Such a peptide linker sequence is incorporated into the fusion protein using standard techniques well known in the art. Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to adopt a flexible extended conformation; (2) their inability to adopt a secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of

hydrophobic or charged residues that might react with the polypeptide functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser residues. Other near neutral amino acids, such as Thr and Ala may also be used in the linker sequence. Amino acid sequences which may be usefully employed as linkers include those disclosed in Maratea *et al.*, *Gene* 40:39-46, 1985; Murphy *et al.*, *Proc. Natl. Acad. Sci. USA* 83:8258-8262, 1986; U.S. Patent No. 4,935,233 and U.S. Patent No. 4,751,180. The linker sequence may generally be from 1 to about 50 amino acids in length. Linker sequences are not required when the first and second polypeptides have non-essential N-terminal amino acid regions that can be used to separate the functional domains and prevent steric interference.

The ligated DNA sequences are operably linked to suitable transcriptional or translational regulatory elements. The regulatory elements responsible for expression of DNA are located only 5' to the DNA sequence encoding the first polypeptides. Similarly, stop codons required to end translation and transcription termination signals are only present 3' to the DNA sequence encoding the second polypeptide.

Fusion proteins are also provided. Such proteins comprise a polypeptide as described herein together with an unrelated immunogenic protein. Preferably the immunogenic protein is capable of eliciting a recall response. Examples of such proteins include tetanus, tuberculosis and hepatitis proteins (*see*, for example, Stoute *et al.* *New Engl. J. Med.*, 336:86-91, 1997).

Within preferred embodiments, an immunological fusion partner is derived from protein D, a surface protein of the gram-negative bacterium *Haemophilus influenza B* (WO 91/18926). Preferably, a protein D derivative comprises approximately the first third of the protein (e.g., the first N-terminal 100-110 amino acids), and a protein D derivative may be lipidated. Within certain preferred embodiments, the first 109 residues of a Lipoprotein D fusion partner is included on the N-terminus to provide the polypeptide with additional exogenous T-cell epitopes and to increase the expression level in *E. coli* (thus functioning as an expression enhancer). The lipid tail ensures optimal presentation of the antigen to antigen presenting cells. Other fusion partners include the non-structural protein

from influenzae virus, NS1 (hemagglutinin). Typically, the N-terminal 81 amino acids are used, although different fragments that include T-helper epitopes may be used.

In another embodiment, the immunological fusion partner is the protein known as LYTA, or a portion thereof (preferably a C-terminal portion). LYTA is derived from *Streptococcus pneumoniae*, which synthesizes an N-acetyl-L-alanine amidase known as amidase LYTA (encoded by the LytA gene; *Gene* 43:265-292, 1986). LYTA is an autolysin that specifically degrades certain bonds in the peptidoglycan backbone. The C-terminal domain of the LYTA protein is responsible for the affinity to the choline or to some choline analogues such as DEAE. This property has been exploited for the development of *E. coli* C-LYTA expressing plasmids useful for expression of fusion proteins. Purification of hybrid proteins containing the C-LYTA fragment at the amino terminus has been described (see *Biotechnology* 10:795-798, 1992). Within a preferred embodiment, a repeat portion of LYTA may be incorporated into a fusion protein. A repeat portion is found in the C-terminal region starting at residue 178. A particularly preferred repeat portion incorporates residues 188-305.

In general, polypeptides (including fusion proteins) and polynucleotides as described herein are isolated. An "isolated" polypeptide or polynucleotide is one that is removed from its original environment. For example, a naturally-occurring protein is isolated if it is separated from some or all of the coexisting materials in the natural system. Preferably, such polypeptides are at least about 90% pure, more preferably at least about 95% pure and most preferably at least about 99% pure. A polynucleotide is considered to be isolated if, for example, it is cloned into a vector that is not a part of the natural environment.

BINDING AGENTS

The present invention further provides agents, such as antibodies and antigen-binding fragments thereof, that specifically bind to a prostate-specific protein. As used herein, an antibody, or antigen-binding fragment thereof, is said to "specifically bind" to a prostate-specific protein if it reacts at a detectable level (within, for example, an

ELISA) with a prostate-specific protein, and does not react detectably with unrelated proteins under similar conditions. As used herein, "binding" refers to a noncovalent association between two separate molecules such that a complex is formed. The ability to bind may be evaluated by, for example, determining a binding constant for the formation of
5 the complex. The binding constant is the value obtained when the concentration of the complex is divided by the product of the component concentrations. In general, two compounds are said to "bind," in the context of the present invention, when the binding constant for complex formation exceeds about 10^3 L/mol. The binding constant may be determined using methods well known in the art.

10 Binding agents may be further capable of differentiating between patients with and without a cancer, such as prostate cancer, using the representative assays provided herein. In other words, antibodies or other binding agents that bind to a prostate-specific protein will generate a signal indicating the presence of a cancer in at least about 20% of patients with the disease, and will generate a negative signal indicating the absence of the
15 disease in at least about 90% of individuals without the cancer. To determine whether a binding agent satisfies this requirement, biological samples (*e.g.*, blood, sera, sputum, urine and/or tumor biopsies) from patients with and without a cancer (as determined using standard clinical tests) may be assayed as described herein for the presence of polypeptides that bind to the binding agent. It will be apparent that a statistically significant number of
20 samples with and without the disease should be assayed. Each binding agent should satisfy the above criteria; however, those of ordinary skill in the art will recognize that binding agents may be used in combination to improve sensitivity.

Any agent that satisfies the above requirements may be a binding agent. For example, a binding agent may be a ribosome, with or without a peptide component, an
25 RNA molecule or a polypeptide. In a preferred embodiment, a binding agent is an antibody or an antigen-binding fragment thereof. Antibodies may be prepared by any of a variety of techniques known to those of ordinary skill in the art. *See, e.g.*, Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In general, antibodies can be produced by cell culture techniques, including the generation of

monoclonal antibodies as described herein, or via transfection of antibody genes into suitable bacterial or mammalian cell hosts, in order to allow for the production of recombinant antibodies. In one technique, an immunogen comprising the polypeptide is initially injected into any of a wide variety of mammals (*e.g.*, mice, rats, rabbits, sheep or goats). In this step, the polypeptides of this invention may serve as the immunogen without modification. Alternatively, particularly for relatively short polypeptides, a superior immune response may be elicited if the polypeptide is joined to a carrier protein, such as bovine serum albumin or keyhole limpet hemocyanin. The immunogen is injected into the animal host, preferably according to a predetermined schedule incorporating one or more booster immunizations, and the animals are bled periodically. Polyclonal antibodies specific for the polypeptide may then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

Monoclonal antibodies specific for an antigenic polypeptide of interest may be prepared, for example, using the technique of Kohler and Milstein, *Eur. J. Immunol.* 6:511-519, 1976, and improvements thereto. Briefly, these methods involve the preparation of immortal cell lines capable of producing antibodies having the desired specificity (*i.e.*, reactivity with the polypeptide of interest). Such cell lines may be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. A variety of fusion techniques may be employed. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine, aminopterin, thymidine) selection. After a sufficient time, usually about 1 to 2 weeks, colonies of hybrids are observed. Single colonies are selected and their culture supernatants tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the

yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction. The polypeptides of this invention may be used in the purification process in, for example, an affinity chromatography step.

Within certain embodiments, the use of antigen-binding fragments of antibodies may be preferred. Such fragments include Fab fragments, which may be prepared using standard techniques. Briefly, immunoglobulins may be purified from rabbit serum by affinity chromatography on Protein A bead columns (Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988) and digested by papain to yield Fab and Fc fragments. The Fab and Fc fragments may be separated by affinity chromatography on protein A bead columns.

Monoclonal antibodies of the present invention may be coupled to one or more therapeutic agents. Suitable agents in this regard include radionuclides, differentiation inducers, drugs, toxins, and derivatives thereof. Preferred radionuclides include ⁹⁰Y, ¹²³I, ¹²⁵I, ¹³¹I, ¹⁸⁶Re, ¹⁸⁸Re, ²¹¹At, and ²¹²Bi. Preferred drugs include methotrexate, and pyrimidine and purine analogs. Preferred differentiation inducers include phorbol esters and butyric acid. Preferred toxins include ricin, abrin, diphtheria toxin, cholera toxin, gelonin, Pseudomonas exotoxin, Shigella toxin, and pokeweed antiviral protein.

A therapeutic agent may be coupled (*e.g.*, covalently bonded) to a suitable monoclonal antibody either directly or indirectly (*e.g.*, via a linker group). A direct reaction between an agent and an antibody is possible when each possesses a substituent capable of reacting with the other. For example, a nucleophilic group, such as an amino or sulphydryl group, on one may be capable of reacting with a carbonyl-containing group, such as an anhydride or an acid halide, or with an alkyl group containing a good leaving group (*e.g.*, a halide) on the other.

Alternatively, it may be desirable to couple a therapeutic agent and an antibody via a linker group. A linker group can function as a spacer to distance an antibody from an agent in order to avoid interference with binding capabilities. A linker group can also serve to increase the chemical reactivity of a substituent on an agent or an antibody, and thus increase the coupling efficiency. An increase in chemical reactivity may also facilitate the use of agents, or functional groups on agents, which otherwise would not be possible.

It will be evident to those skilled in the art that a variety of bifunctional or polyfunctional reagents, both homo- and hetero-functional (such as those described in the catalog of the Pierce Chemical Co., Rockford, IL), may be employed as the linker group. Coupling may be effected, for example, through amino groups, carboxyl groups, sulphydryl groups or oxidized carbohydrate residues. There are numerous references describing such methodology, *e.g.*, U.S. Patent No. 4,671,958, to Rodwell *et al.*

Where a therapeutic agent is more potent when free from the antibody portion of the immunoconjugates of the present invention, it may be desirable to use a linker group which is cleavable during or upon internalization into a cell. A number of different cleavable linker groups have been described. The mechanisms for the intracellular release of an agent from these linker groups include cleavage by reduction of a disulfide bond (*e.g.*, U.S. Patent No. 4,489,710, to Spitzer), by irradiation of a photolabile bond (*e.g.*, U.S. Patent No. 4,625,014, to Senter *et al.*), by hydrolysis of derivatized amino acid side chains (*e.g.*, U.S. Patent No. 4,638,045, to Kohn *et al.*), by serum complement-mediated hydrolysis (*e.g.*, U.S. Patent No. 4,671,958, to Rodwell *et al.*), and acid-catalyzed hydrolysis (*e.g.*, U.S. Patent No. 4,569,789, to Blattler *et al.*).

It may be desirable to couple more than one agent to an antibody. In one embodiment, multiple molecules of an agent are coupled to one antibody molecule. In another embodiment, more than one type of agent may be coupled to one antibody. Regardless of the particular embodiment, immunoconjugates with more than one agent may be prepared in a variety of ways. For example, more than one agent may be coupled

directly to an antibody molecule, or linkers that provide multiple sites for attachment can be used. Alternatively, a carrier can be used.

A carrier may bear the agents in a variety of ways, including covalent bonding either directly or via a linker group. Suitable carriers include proteins such as albumins (e.g., U.S. Patent No. 4,507,234, to Kato *et al.*), peptides and polysaccharides such as aminodextran (e.g., U.S. Patent No. 4,699,784, to Shih *et al.*). A carrier may also bear an agent by noncovalent bonding or by encapsulation, such as within a liposome vesicle (e.g., U.S. Patent Nos. 4,429,008 and 4,873,088). Carriers specific for radionuclide agents include radiohalogenated small molecules and chelating compounds. For example, 10 U.S. Patent No. 4,735,792 discloses representative radiohalogenated small molecules and their synthesis. A radionuclide chelate may be formed from chelating compounds that include those containing nitrogen and sulfur atoms as the donor atoms for binding the metal, or metal oxide, radionuclide. For example, U.S. Patent No. 4,673,562, to Davison *et al.* discloses representative chelating compounds and their synthesis.

15 A variety of routes of administration for the antibodies and immunoconjugates may be used. Typically, administration will be intravenous, intramuscular, subcutaneous or in the bed of a resected tumor. It will be evident that the precise dose of the antibody/immunoconjugate will vary depending upon the antibody used, the antigen density on the tumor, and the rate of clearance of the antibody.

20 T CELLS

Immunotherapeutic compositions may also, or alternatively, comprise T cells specific for a prostate-specific protein. Such cells may generally be prepared *in vitro* or *ex vivo*, using standard procedures. For example, T cells may be isolated from bone marrow, peripheral blood, or a fraction of bone marrow or peripheral blood of a patient, 25 using a commercially available cell separation system, such as the Isolex™ System, available from Nexell Therapeutics, Inc. (Irvine, CA; see also U.S. Patent No. 5,240,856; U.S. Patent No. 5,215,926; WO 89/06280; WO 91/16116 and WO 92/07243).

Alternatively, T cells may be derived from related or unrelated humans, non-human mammals, cell lines or cultures.

T cells may be stimulated with a prostate-specific polypeptide, polynucleotide encoding a prostate-specific polypeptide and/or an antigen presenting cell (APC) that expresses such a polypeptide. Such stimulation is performed under conditions and for a time sufficient to permit the generation of T cells that are specific for the polypeptide. Preferably, a prostate-specific polypeptide or polynucleotide is present within a delivery vehicle, such as a microsphere, to facilitate the generation of specific T cells.

T cells are considered to be specific for a prostate-specific polypeptide if the T cells specifically proliferate, secrete cytokines or kill target cells coated with the polypeptide or expressing a gene encoding the polypeptide. T cell specificity may be evaluated using any of a variety of standard techniques. For example, within a chromium release assay or proliferation assay, a stimulation index of more than two fold increase in lysis and/or proliferation, compared to negative controls, indicates T cell specificity. Such assays may be performed, for example, as described in Chen *et al.*, *Cancer Res.* 54:1065-1070, 1994. Alternatively, detection of the proliferation of T cells may be accomplished by a variety of known techniques. For example, T cell proliferation can be detected by measuring an increased rate of DNA synthesis (*e.g.*, by pulse-labeling cultures of T cells with tritiated thymidine and measuring the amount of tritiated thymidine incorporated into DNA). Contact with a prostate-specific polypeptide (100 ng/ml - 100 µg/ml, preferably 200 ng/ml - 25 µg/ml) for 3 - 7 days should result in at least a two fold increase in proliferation of the T cells. Contact as described above for 2-3 hours should result in activation of the T cells, as measured using standard cytokine assays in which a two fold increase in the level of cytokine release (*e.g.*, TNF or IFN- γ) is indicative of T cell activation (*see* Coligan *et al.*, *Current Protocols in Immunology*, vol. 1, Wiley Interscience (Greene 1998)). T cells that have been activated in response to a prostate-specific polypeptide, polynucleotide or polypeptide-expressing APC may be CD4 $^{+}$ and/or CD8 $^{+}$. prostate-specific protein-specific T cells may be expanded using standard techniques.

Within preferred embodiments, the T cells are derived from a patient, a related donor or an unrelated donor, and are administered to the patient following stimulation and expansion.

For therapeutic purposes, CD4⁺ or CD8⁺ T cells that proliferate in response to a prostate-specific polypeptide, polynucleotide or APC can be expanded in number either *in vitro* or *in vivo*. Proliferation of such T cells *in vitro* may be accomplished in a variety of ways. For example, the T cells can be re-exposed to a prostate-specific polypeptide, or a short peptide corresponding to an immunogenic portion of such a polypeptide, with or without the addition of T cell growth factors, such as interleukin-2, and/or stimulator cells that synthesize a prostate-specific polypeptide. Alternatively, one or more T cells that proliferate in the presence of a prostate-specific protein can be expanded in number by cloning. Methods for cloning cells are well known in the art, and include limiting dilution.

PHARMACEUTICAL COMPOSITIONS

In additional embodiments, the present invention concerns formulation of one or more of the polynucleotide, polypeptide, T-cell and/or antibody compositions disclosed herein in pharmaceutically-acceptable solutions for administration to a cell or an animal, either alone, or in combination with one or more other modalities of therapy.

It will also be understood that, if desired, the nucleic acid segment, RNA, DNA or PNA compositions that express a polypeptide as disclosed herein may be administered in combination with other agents as well, such as, *e.g.*, other proteins or polypeptides or various pharmaceutically-active agents. In fact, there is virtually no limit to other components that may also be included, given that the additional agents do not cause a significant adverse effect upon contact with the target cells or host tissues. The compositions may thus be delivered along with various other agents as required in the particular instance. Such compositions may be purified from host cells or other biological sources, or alternatively may be chemically synthesized as described herein. Likewise, such compositions may further comprise substituted or derivatized RNA or DNA compositions.

Formulation of pharmaceutically-acceptable excipients and carrier solutions is well-known to those of skill in the art, as is the development of suitable dosing and treatment regimens for using the particular compositions described herein in a variety of treatment regimens, including *e.g.*, oral, parenteral, intravenous, intranasal, and 5 intramuscular administration and formulation.

1. ORAL DELIVERY

In certain applications, the pharmaceutical compositions disclosed herein may be delivered *via* oral administration to an animal. As such, these compositions may be formulated with an inert diluent or with an assimilable edible carrier, or they may be 10 enclosed in hard- or soft-shell gelatin capsule, or they may be compressed into tablets, or they may be incorporated directly with the food of the diet.

The active compounds may even be incorporated with excipients and used in the form of ingestible tablets, buccal tables, troches, capsules, elixirs, suspensions, syrups, wafers, and the like (Mathiowitz *et al.*, 1997; Hwang *et al.*, 1998; U. S. Patent 15 5,641,515; U. S. Patent 5,580,579 and U. S. Patent 5,792,451, each specifically incorporated herein by reference in its entirety). The tablets, troches, pills, capsules and the like may also contain the following: a binder, as gum tragacanth, acacia, cornstarch, or gelatin; excipients, such as dicalcium phosphate; a disintegrating agent, such as corn starch, potato starch, alginic acid and the like; a lubricant, such as magnesium stearate; and a 20 sweetening agent, such as sucrose, lactose or saccharin may be added or a flavoring agent, such as peppermint, oil of wintergreen, or cherry flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar, or 25 both. A syrup of elixir may contain the active compound sucrose as a sweetening agent methyl and propylparabens as preservatives, a dye and flavoring, such as cherry or orange flavor. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed. In addition,

the active compounds may be incorporated into sustained-release preparation and formulations.

Typically, these formulations may contain at least about 0.1% of the active compound or more, although the percentage of the active ingredient(s) may, of course, be varied and may conveniently be between about 1 or 2% and about 60% or 70% or more of the weight or volume of the total formulation. Naturally, the amount of active compound(s) in each therapeutically useful composition may be prepared in such a way that a suitable dosage will be obtained in any given unit dose of the compound. Factors such as solubility, bioavailability, biological half-life, route of administration, product shelf life, as well as other pharmacological considerations will be contemplated by one skilled in the art of preparing such pharmaceutical formulations, and as such, a variety of dosages and treatment regimens may be desirable.

For oral administration the compositions of the present invention may alternatively be incorporated with one or more excipients in the form of a mouthwash, dentifrice, buccal tablet, oral spray, or sublingual orally-administered formulation. For example, a mouthwash may be prepared incorporating the active ingredient in the required amount in an appropriate solvent, such as a sodium borate solution (Dobell's Solution). Alternatively, the active ingredient may be incorporated into an oral solution such as one containing sodium borate, glycerin and potassium bicarbonate, or dispersed in a dentifrice, or added in a therapeutically-effective amount to a composition that may include water, binders, abrasives, flavoring agents, foaming agents, and humectants. Alternatively the compositions may be fashioned into a tablet or solution form that may be placed under the tongue or otherwise dissolved in the mouth.

2. INJECTABLE DELIVERY

In certain circumstances it will be desirable to deliver the pharmaceutical compositions disclosed herein parenterally, intravenously, intramuscularly, or even intraperitoneally as described in U. S. Patent 5,543,158; U. S. Patent 5,641,515 and U. S. Patent 5,399,363 (each specifically incorporated herein by reference in its entirety).

Solutions of the active compounds as free base or pharmacologically acceptable salts may be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions may also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations 5 contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions (U. S. Patent 5,466,468, specifically incorporated herein by reference in its entirety). In all cases the form must be sterile and must be fluid to the 10 extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (*e.g.*, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and/or vegetable oils. Proper 15 fluidity may be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be facilitated by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic 20 agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

For parenteral administration in an aqueous solution, for example, the solution should be suitably buffered if necessary and the liquid diluent first rendered 25 isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. In this connection, a sterile aqueous medium that can be employed will be known to those of skill in the art in light of the present disclosure. For example, one dosage may be dissolved in 1 ml of isotonic NaCl solution and either added to 1000 ml of hypodermoclysis fluid or

injected at the proposed site of infusion, (see for example, "Remington's Pharmaceutical Sciences" 15th Edition, pages 1035-1038 and 1570-1580). Some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject. Moreover, for human administration, preparations should meet sterility, pyrogenicity, and the general safety and purity standards as required by FDA Office of Biologics standards.

Sterile injectable solutions are prepared by incorporating the active compounds in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

The compositions disclosed herein may be formulated in a neutral or salt form. Pharmaceutically-acceptable salts, include the acid addition salts (formed with the free amino groups of the protein) and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like. Upon formulation, solutions will be administered in a manner compatible with the dosage formulation and in such amount as is therapeutically effective. The formulations are easily administered in a variety of dosage forms such as injectable solutions, drug-release capsules, and the like.

As used herein, "carrier" includes any and all solvents, dispersion media, vehicles, coatings, diluents, antibacterial and antifungal agents, isotonic and absorption

delaying agents, buffers, carrier solutions, suspensions, colloids, and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active 5 ingredients can also be incorporated into the compositions.

The phrase "pharmaceutically-acceptable" refers to molecular entities and compositions that do not produce an allergic or similar untoward reaction when administered to a human. The preparation of an aqueous composition that contains a protein as an active ingredient is well understood in the art. Typically, such compositions 10 are prepared as injectables, either as liquid solutions or suspensions; solid forms suitable for solution in, or suspension in, liquid prior to injection can also be prepared. The preparation can also be emulsified.

3. NASAL DELIVERY

In certain embodiments, the pharmaceutical compositions may be delivered 15 by intranasal sprays, inhalation, and/or other aerosol delivery vehicles. Methods for delivering genes, nucleic acids, and peptide compositions directly to the lungs *via* nasal aerosol sprays has been described *e.g.*, in U. S. Patent 5,756,353 and U. S. Patent 5,804,212 (each specifically incorporated herein by reference in its entirety). Likewise, the delivery 20 of drugs using intranasal microparticle resins (Takenaga *et al.*, 1998) and lysophosphatidyl-glycerol compounds (U. S. Patent 5,725,871, specifically incorporated herein by reference in its entirety) are also well-known in the pharmaceutical arts. Likewise, transmucosal drug delivery in the form of a polytetrafluoroethylene support matrix is described in U. S. Patent 5,780,045 (specifically incorporated herein by reference in its entirety).

4. LIPOSOME-, NANOCAPSULE-, AND MICROPARTICLE-MEDIATED DELIVERY

25 In certain embodiments, the inventors contemplate the use of liposomes, nanocapsules, microparticles, microspheres, lipid particles, vesicles, and the like, for the introduction of the compositions of the present invention into suitable host cells. In

particular, the compositions of the present invention may be formulated for delivery either encapsulated in a lipid particle, a liposome, a vesicle, a nanosphere, or a nanoparticle or the like.

Such formulations may be preferred for the introduction of pharmaceutically-acceptable formulations of the nucleic acids or constructs disclosed herein. The formation and use of liposomes is generally known to those of skill in the art (see for example, Couvreur *et al.*, 1977; Couvreur, 1988; Lasic, 1998; which describes the use of liposomes and nanocapsules in the targeted antibiotic therapy for intracellular bacterial infections and diseases). Recently, liposomes were developed with improved serum stability and circulation half-times (Gabizon and Papahadjopoulos, 1988; Allen and Choun, 1987; U. S. Patent 5,741,516, specifically incorporated herein by reference in its entirety). Further, various methods of liposome and liposome like preparations as potential drug carriers have been reviewed (Takakura, 1998; Chandran *et al.*, 1997; Margalit, 1995; U. S. Patent 5,567,434; U. S. Patent 5,552,157; U. S. Patent 5,565,213; U. S. Patent 5,738,868 and U. S. Patent 5,795,587, each specifically incorporated herein by reference in its entirety).

Liposomes have been used successfully with a number of cell types that are normally resistant to transfection by other procedures including T cell suspensions, primary hepatocyte cultures and PC 12 cells (Renneisen *et al.*, 1990; Muller *et al.*, 1990). In addition, liposomes are free of the DNA length constraints that are typical of viral-based delivery systems. Liposomes have been used effectively to introduce genes, drugs (Heath and Martin, 1986; Heath *et al.*, 1986; Balazssovits *et al.*, 1989; Fresta and Puglisi, 1996), radiotherapeutic agents (Pikul *et al.*, 1987), enzymes (Imaizumi *et al.*, 1990a; Imaizumi *et al.*, 1990b), viruses (Faller and Baltimore, 1984), transcription factors and allosteric effectors (Nicolau and Gersonde, 1979) into a variety of cultured cell lines and animals. In addition, several successful clinical trials examining the effectiveness of liposome-mediated drug delivery have been completed (Lopez-Berestein *et al.*, 1985a; 1985b; Coune, 1988; Sculier *et al.*, 1988). Furthermore, several studies suggest that the use of

liposomes is not associated with autoimmune responses, toxicity or gonadal localization after systemic delivery (Mori and Fukatsu, 1992).

Liposomes are formed from phospholipids that are dispersed in an aqueous medium and spontaneously form multilamellar concentric bilayer vesicles (also termed 5 multilamellar vesicles (MLVs). MLVs generally have diameters of from 25 nm to 4 μm . Sonication of MLVs results in the formation of small unilamellar vesicles (SUVs) with diameters in the range of 200 to 500 Å, containing an aqueous solution in the core.

Liposomes bear resemblance to cellular membranes and are contemplated for use in connection with the present invention as carriers for the peptide compositions.

10 They are widely suitable as both water- and lipid-soluble substances can be entrapped, *i.e.* in the aqueous spaces and within the bilayer itself, respectively. It is possible that the drug-bearing liposomes may even be employed for site-specific delivery of active agents by selectively modifying the liposomal formulation.

In addition to the teachings of Couvreur *et al.* (1977; 1988), the following 15 information may be utilized in generating liposomal formulations. Phospholipids can form a variety of structures other than liposomes when dispersed in water, depending on the molar ratio of lipid to water. At low ratios the liposome is the preferred structure. The physical characteristics of liposomes depend on pH, ionic strength and the presence of divalent cations. Liposomes can show low permeability to ionic and polar substances, but 20 at elevated temperatures undergo a phase transition which markedly alters their permeability. The phase transition involves a change from a closely packed, ordered structure, known as the gel state, to a loosely packed, less-ordered structure, known as the fluid state. This occurs at a characteristic phase-transition temperature and results in an increase in permeability to ions, sugars and drugs.

25 In addition to temperature, exposure to proteins can alter the permeability of liposomes. Certain soluble proteins, such as cytochrome c, bind, deform and penetrate the bilayer, thereby causing changes in permeability. Cholesterol inhibits this penetration of proteins, apparently by packing the phospholipids more tightly. It is contemplated that the

most useful liposome formations for antibiotic and inhibitor delivery will contain cholesterol.

The ability to trap solutes varies between different types of liposomes. For example, MLVs are moderately efficient at trapping solutes, but SUVs are extremely 5 inefficient. SUVs offer the advantage of homogeneity and reproducibility in size distribution, however, and a compromise between size and trapping efficiency is offered by large unilamellar vesicles (LUVs). These are prepared by ether evaporation and are three to four times more efficient at solute entrapment than MLVs.

In addition to liposome characteristics, an important determinant in 10 entrapping compounds is the physicochemical properties of the compound itself. Polar compounds are trapped in the aqueous spaces and nonpolar compounds bind to the lipid bilayer of the vesicle. Polar compounds are released through permeation or when the bilayer is broken, but nonpolar compounds remain affiliated with the bilayer unless it is disrupted by temperature or exposure to lipoproteins. Both types show maximum efflux 15 rates at the phase transition temperature.

Liposomes interact with cells *via* four different mechanisms: endocytosis by phagocytic cells of the reticuloendothelial system such as macrophages and neutrophils; adsorption to the cell surface, either by nonspecific weak hydrophobic or electrostatic forces, or by specific interactions with cell-surface components; fusion with the plasma cell 20 membrane by insertion of the lipid bilayer of the liposome into the plasma membrane, with simultaneous release of liposomal contents into the cytoplasm; and by transfer of liposomal lipids to cellular or subcellular membranes, or vice versa, without any association of the liposome contents. It often is difficult to determine which mechanism is operative and more than one may operate at the same time.

25 The fate and disposition of intravenously injected liposomes depend on their physical properties, such as size, fluidity, and surface charge. They may persist in tissues for h or days, depending on their composition, and half lives in the blood range from min to several h. Larger liposomes, such as MLVs and LUVs, are taken up rapidly by phagocytic cells of the reticuloendothelial system, but physiology of the circulatory system restrains

the exit of such large species at most sites. They can exit only in places where large openings or pores exist in the capillary endothelium, such as the sinusoids of the liver or spleen. Thus, these organs are the predominate site of uptake. On the other hand, SUVs show a broader tissue distribution but still are sequestered highly in the liver and spleen. In 5 general, this *in vivo* behavior limits the potential targeting of liposomes to only those organs and tissues accessible to their large size. These include the blood, liver, spleen, bone marrow, and lymphoid organs.

Targeting is generally not a limitation in terms of the present invention. However, should specific targeting be desired, methods are available for this to be 10 accomplished. Antibodies may be used to bind to the liposome surface and to direct the antibody and its drug contents to specific antigenic receptors located on a particular cell-type surface. Carbohydrate determinants (glycoprotein or glycolipid cell-surface components that play a role in cell-cell recognition, interaction and adhesion) may also be used as recognition sites as they have potential in directing liposomes to particular cell 15 types. Mostly, it is contemplated that intravenous injection of liposomal preparations would be used, but other routes of administration are also conceivable.

Alternatively, the invention provides for pharmaceutically-acceptable nanocapsule formulations of the compositions of the present invention. Nanocapsules can generally entrap compounds in a stable and reproducible way (Henry-Michelland *et al.*, 20 1987; Quintanar-Guerrero *et al.*, 1998; Douglas *et al.*, 1987). To avoid side effects due to intracellular polymeric overloading, such ultrafine particles (sized around 0.1 μm) should be designed using polymers able to be degraded *in vivo*. Biodegradable polyalkyl-cyanoacrylate nanoparticles that meet these requirements are contemplated for use in the present invention. Such particles may be easily made, as described (Couvreur *et al.*, 25 1980; 1988; zur Muhlen *et al.*, 1998; Zambaux *et al.* 1998; Pinto-Alphandry *et al.*, 1995 and U. S. Patent 5,145,684, specifically incorporated herein by reference in its entirety).

IMMUNOGENIC COMPOSITIONS

In certain preferred embodiments of the present invention, immunogenic compositions, or vaccines, are provided. The immunogenic compositions will generally comprise one or more pharmaceutical compositions, such as those discussed above, in combination with an immunostimulant. An immunostimulant may be any substance that enhances or potentiates an immune response (antibody and/or cell-mediated) to an exogenous antigen. Examples of immunostimulants include adjuvants, biodegradable microspheres (*e.g.*, polylactic galactide) and liposomes (into which the compound is incorporated; *see e.g.*, Fullerton, U.S. Patent No. 4,235,877). Vaccine preparation is generally described in, for example, M.F. Powell and M.J. Newman, eds., "Vaccine Design (the subunit and adjuvant approach)," Plenum Press (NY, 1995). Pharmaceutical compositions and immunogenic compositions within the scope of the present invention may also contain other compounds, which may be biologically active or inactive. For example, one or more immunogenic portions of other tumor antigens may be present, either incorporated into a fusion polypeptide or as a separate compound, within the composition.

Illustrative immunogenic compositions may contain DNA encoding one or more of the polypeptides as described above, such that the polypeptide is generated *in situ*. As noted above, the DNA may be present within any of a variety of delivery systems known to those of ordinary skill in the art, including nucleic acid expression systems, bacteria and viral expression systems. Numerous gene delivery techniques are well known in the art, such as those described by Rolland, *Crit. Rev. Therap. Drug Carrier Systems* 15:143-198, 1998, and references cited therein. Appropriate nucleic acid expression systems contain the necessary DNA sequences for expression in the patient (such as a suitable promoter and terminating signal). Bacterial delivery systems involve the administration of a bacterium (such as *Bacillus-Calmette-Guerrin*) that expresses an immunogenic portion of the polypeptide on its cell surface or secretes such an epitope. In a preferred embodiment, the DNA may be introduced using a viral expression system (*e.g.*, vaccinia or other pox virus, retrovirus, or adenovirus), which may involve the use of a non-pathogenic (defective), replication competent virus. Suitable systems are disclosed, for

example, in Fisher-Hoch *et al.*, *Proc. Natl. Acad. Sci. USA* 86:317-321, 1989; Flexner *et al.*, *Ann. N.Y. Acad. Sci.* 569:86-103, 1989; Flexner *et al.*, *Vaccine* 8:17-21, 1990; U.S. Patent Nos. 4,603,112, 4,769,330, and 5,017,487; WO 89/01973; U.S. Patent No. 4,777,127; GB 2,200,651; EP 0,345,242; WO 91/02805; Berkner, *Biotechniques* 5:616-627, 1988; Rosenfeld *et al.*, *Science* 252:431-434, 1991; Kolls *et al.*, *Proc. Natl. Acad. Sci. USA* 91:215-219, 1994; Kass-Eisler *et al.*, *Proc. Natl. Acad. Sci. USA* 90:11498-11502, 1993; Guzman *et al.*, *Circulation* 88:2838-2848, 1993; and Guzman *et al.*, *Cir. Res.* 73:1202-1207, 1993. Techniques for incorporating DNA into such expression systems are well known to those of ordinary skill in the art. The DNA may also be 10 "naked," as described, for example, in Ulmer *et al.*, *Science* 259:1745-1749, 1993 and reviewed by Cohen, *Science* 259:1691-1692, 1993. The uptake of naked DNA may be increased by coating the DNA onto biodegradable beads, which are efficiently transported into the cells. It will be apparent that an immunogenic composition may comprise both a polynucleotide and a polypeptide component. Such immunogenic compositions may 15 provide for an enhanced immune response.

It will be apparent that an immunogenic composition may contain pharmaceutically acceptable salts of the polynucleotides and polypeptides provided herein. Such salts may be prepared from pharmaceutically acceptable non-toxic bases, including organic bases (e.g., salts of primary, secondary and tertiary amines and basic amino acids) 20 and inorganic bases (e.g., sodium, potassium, lithium, ammonium, calcium and magnesium salts).

While any suitable carrier known to those of ordinary skill in the art may be employed in the compositions of this invention, the type of carrier will vary depending on the mode of administration. Compositions of the present invention may be formulated for 25 any appropriate manner of administration, including for example, topical, oral, nasal, intravenous, intracranial, intraperitoneal, subcutaneous or intramuscular administration. For parenteral administration, such as subcutaneous injection, the carrier preferably comprises water, saline, alcohol, a fat, a wax or a buffer. For oral administration, any of the above carriers or a solid carrier, such as mannitol, lactose, starch, magnesium stearate,

sodium saccharine, talcum, cellulose, glucose, sucrose, and magnesium carbonate, may be employed. Biodegradable microspheres (*e.g.*, polylactate polyglycolate) may also be employed as carriers for the pharmaceutical compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S. Patent Nos. 4,897,268; 5,075,109; 5,928,647; 5,811,128; 5,820,883; 5,853,763; 5,814,344 and 5,942,252. One may also employ a carrier comprising the particulate-protein complexes described in U.S. Patent No. 5,928,647, which are capable of inducing a class I-restricted cytotoxic T lymphocyte responses in a host.

Such compositions may also comprise buffers (*e.g.*, neutral buffered saline or phosphate buffered saline), carbohydrates (*e.g.*, glucose, mannose, sucrose or dextrans), mannitol, proteins, polypeptides or amino acids such as glycine, antioxidants, bacteriostats, chelating agents such as EDTA or glutathione, adjuvants (*e.g.*, aluminum hydroxide), solutes that render the formulation isotonic, hypotonic or weakly hypertonic with the blood of a recipient, suspending agents, thickening agents and/or preservatives. Alternatively, compositions of the present invention may be formulated as a lyophilizate. Compounds may also be encapsulated within liposomes using well known technology.

Any of a variety of immunostimulants may be employed in the immunogenic compositions of this invention. For example, an adjuvant may be included. Most adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a stimulator of immune responses, such as lipid A, *Bordetella pertussis* or *Mycobacterium tuberculosis* derived proteins. Suitable adjuvants are commercially available as, for example, Freund's Incomplete Adjuvant and Complete Adjuvant (Difco Laboratories, Detroit, MI); Merck Adjuvant 65 (Merck and Company, Inc., Rahway, NJ); AS-2 (SmithKline Beecham, Philadelphia, PA); aluminum salts such as aluminum hydroxide gel (alum) or aluminum phosphate; salts of calcium, iron or zinc; an insoluble suspension of acylated tyrosine; acylated sugars; cationically or anionically derivatized polysaccharides; polyphosphazenes; biodegradable microspheres; monophosphoryl lipid A and quil A. Cytokines, such as GM-CSF or interleukin-2, -7, or -12, may also be used as adjuvants.

Within the immunogenic compositions provided herein, the adjuvant composition is preferably designed to induce an immune response predominantly of the Th1 type. High levels of Th1-type cytokines (e.g., IFN- γ , TNF α , IL-2 and IL-12) tend to favor the induction of cell mediated immune responses to an administered antigen. In contrast, high levels of Th2-type cytokines (e.g., IL-4, IL-5, IL-6 and IL-10) tend to favor the induction of humoral immune responses. Following application of an immunogenic composition as provided herein, a patient will support an immune response that includes Th1- and Th2-type responses. Within a preferred embodiment, in which a response is predominantly Th1-type, the level of Th1-type cytokines will increase to a greater extent than the level of Th2-type cytokines. The levels of these cytokines may be readily assessed using standard assays. For a review of the families of cytokines, see Mosmann and Coffman, *Ann. Rev. Immunol.* 7:145-173, 1989.

Preferred adjuvants for use in eliciting a predominantly Th1-type response include, for example, a combination of monophosphoryl lipid A, preferably 3-de-O-acylated monophosphoryl lipid A (3D-MPL), together with an aluminum salt. MPL adjuvants are available from Corixa Corporation (Seattle, WA; *see* US Patent Nos. 4,436,727; 4,877,611; 4,866,034 and 4,912,094). CpG-containing oligonucleotides (in which the CpG dinucleotide is unmethylated) also induce a predominantly Th1 response. Such oligonucleotides are well known and are described, for example, in WO 96/02555, WO 99/33488 and U.S. Patent Nos. 6,008,200 and 5,856,462. Immunostimulatory DNA sequences are also described, for example, by Sato *et al.*, *Science* 273:352, 1996. Another preferred adjuvant is a saponin, preferably QS21 (Aquila Biopharmaceuticals Inc., Framingham, MA), which may be used alone or in combination with other adjuvants. For example, an enhanced system involves the combination of a monophosphoryl lipid A and saponin derivative, such as the combination of QS21 and 3D-MPL as described in WO 94/00153, or a less reactogenic composition where the QS21 is quenched with cholesterol, as described in WO 96/33739. Other preferred formulations comprise an oil-in-water emulsion and tocopherol. A particularly potent adjuvant formulation involving QS21, 3D-MPL and tocopherol in an oil-in-water emulsion is described in WO 95/17210.

Other preferred adjuvants include Montanide ISA 720 (Seppic, France), SAF (Chiron, California, United States), ISCOMS (CSL), MF-59 (Chiron), the SBAS series of adjuvants (*e.g.*, SBAS-2 or SBAS-4, available from SmithKline Beecham, Rixensart, Belgium), Detox (Corixa, Hamilton, MT), RC-529 (Corixa, Hamilton, MT) and 5 other aminoalkyl glucosaminide 4-phosphates (AGPs), such as those described in pending U.S. Patent Application Serial Nos. 08/853,826 and 09/074,720, the disclosures of which are incorporated herein by reference in their entireties.

Any immunogenic composition provided herein may be prepared using well known methods that result in a combination of antigen, immune response enhancer and a 10 suitable carrier or excipient. The compositions described herein may be administered as part of a sustained release formulation (*i.e.*, a formulation such as a capsule, sponge or gel (composed of polysaccharides, for example) that effects a slow release of compound following administration). Such formulations may generally be prepared using well known technology (*see, e.g.*, Coombes *et al.*, *Vaccine* 14:1429-1438, 1996) and administered by, 15 for example, oral, rectal or subcutaneous implantation, or by implantation at the desired target site. Sustained-release formulations may contain a polypeptide, polynucleotide or antibody dispersed in a carrier matrix and/or contained within a reservoir surrounded by a rate controlling membrane.

Carriers for use within such formulations are biocompatible, and may also 20 be biodegradable; preferably the formulation provides a relatively constant level of active component release. Such carriers include microparticles of poly(lactide-co-glycolide), polyacrylate, latex, starch, cellulose, dextran and the like. Other delayed-release carriers include supramolecular biovectors, which comprise a non-liquid hydrophilic core (*e.g.*, a cross-linked polysaccharide or oligosaccharide) and, optionally, an external layer 25 comprising an amphiphilic compound, such as a phospholipid (*see e.g.*, U.S. Patent No. 5,151,254 and PCT applications WO 94/20078, WO/94/23701 and WO 96/06638). The amount of active compound contained within a sustained release formulation depends upon the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

Any of a variety of delivery vehicles may be employed within pharmaceutical compositions and immunogenic compositions to facilitate production of an antigen-specific immune response that targets tumor cells. Delivery vehicles include antigen presenting cells (APCs), such as dendritic cells, macrophages, B cells, monocytes 5 and other cells that may be engineered to be efficient APCs. Such cells may, but need not, be genetically modified to increase the capacity for presenting the antigen, to improve activation and/or maintenance of the T cell response, to have anti-tumor effects *per se* and/or to be immunologically compatible with the receiver (*i.e.*, matched HLA haplotype). APCs may generally be isolated from any of a variety of biological fluids and organs, 10 including tumor and peritumoral tissues, and may be autologous, allogeneic, syngeneic or xenogeneic cells.

Certain preferred embodiments of the present invention use dendritic cells or progenitors thereof as antigen-presenting cells. Dendritic cells are highly potent APCs (Banchereau and Steinman, *Nature* 392:245-251, 1998) and have been shown to be 15 effective as a physiological adjuvant for eliciting prophylactic or therapeutic antitumor immunity (see Timmerman and Levy, *Ann. Rev. Med.* 50:507-529, 1999). In general, dendritic cells may be identified based on their typical shape (stellate *in situ*, with marked cytoplasmic processes (dendrites) visible *in vitro*), their ability to take up, process and present antigens with high efficiency and their ability to activate naïve T cell responses. 20 Dendritic cells may, of course, be engineered to express specific cell-surface receptors or ligands that are not commonly found on dendritic cells *in vivo* or *ex vivo*, and such modified dendritic cells are contemplated by the present invention. As an alternative to dendritic cells, secreted vesicles antigen-loaded dendritic cells (called exosomes) may be used within an immunogenic composition (see Zitvogel *et al.*, *Nature Med.* 4:594-600, 25 1998).

Dendritic cells and progenitors may be obtained from peripheral blood, bone marrow, tumor-infiltrating cells, peritumoral tissues-infiltrating cells, lymph nodes, spleen, skin, umbilical cord blood or any other suitable tissue or fluid. For example, dendritic cells may be differentiated *ex vivo* by adding a combination of cytokines such as GM-CSF, IL-4,

IL-13 and/or TNF α to cultures of monocytes harvested from peripheral blood. Alternatively, CD34 positive cells harvested from peripheral blood, umbilical cord blood or bone marrow may be differentiated into dendritic cells by adding to the culture medium combinations of GM-CSF, IL-3, TNF α , CD40 ligand, LPS, flt3 ligand and/or other compound(s) that induce differentiation, maturation and proliferation of dendritic cells.

Dendritic cells are conveniently categorized as "immature" and "mature" cells, which allows a simple way to discriminate between two well characterized phenotypes. However, this nomenclature should not be construed to exclude all possible intermediate stages of differentiation. Immature dendritic cells are characterized as APC 10 with a high capacity for antigen uptake and processing, which correlates with the high expression of Fc γ receptor and mannose receptor. The mature phenotype is typically characterized by a lower expression of these markers, but a high expression of cell surface molecules responsible for T cell activation such as class I and class II MHC, adhesion molecules (*e.g.*, CD54 and CD11) and costimulatory molecules (*e.g.*, CD40, CD80, CD86 15 and 4-1BB).

APCs may generally be transfected with a polynucleotide encoding a prostate-specific protein (or portion or other variant thereof) such that the prostate-specific polypeptide, or an immunogenic portion thereof, is expressed on the cell surface. Such transfection may take place *ex vivo*, and a composition comprising such transfected cells 20 may then be used for therapeutic purposes, as described herein. Alternatively, a gene delivery vehicle that targets a dendritic or other antigen presenting cell may be administered to a patient, resulting in transfection that occurs *in vivo*. *In vivo* and *ex vivo* transfection of dendritic cells, for example, may generally be performed using any methods known in the art, such as those described in WO 97/24447, or the gene gun approach 25 described by Mahvi *et al.*, *Immunology and cell Biology* 75:456-460, 1997. Antigen loading of dendritic cells may be achieved by incubating dendritic cells or progenitor cells with the prostate-specific polypeptide, DNA (naked or within a plasmid vector) or RNA; or with antigen-expressing recombinant bacterium or viruses (*e.g.*, vaccinia, fowlpox, adenovirus or lentivirus vectors). Prior to loading, the polypeptide may be covalently

conjugated to an immunological partner that provides T cell help (e.g., a carrier molecule). Alternatively, a dendritic cell may be pulsed with a non-conjugated immunological partner, separately or in the presence of the polypeptide.

Immunogenic compositions and pharmaceutical compositions may be
5 presented in unit-dose or multi-dose containers, such as sealed ampoules or vials. Such containers are preferably hermetically sealed to preserve sterility of the formulation until use. In general, formulations may be stored as suspensions, solutions or emulsions in oily or aqueous vehicles. Alternatively, a immunogenic composition or pharmaceutical composition may be stored in a freeze-dried condition requiring only the addition of a
10 sterile liquid carrier immediately prior to use.

CANCER THERAPY

In further aspects of the present invention, the compositions described herein may be used for immunotherapy of cancer, such as prostate cancer. Within such methods, pharmaceutical compositions and immunogenic compositions are typically
15 administered to a patient. As used herein, a “patient” refers to any warm-blooded animal, preferably a human. A patient may or may not be afflicted with cancer. Accordingly, the above pharmaceutical compositions and immunogenic compositions may be used to prevent the development of a cancer or to treat a patient afflicted with a cancer. A cancer may be diagnosed using criteria generally accepted in the art, including the presence of a
20 malignant tumor. Pharmaceutical compositions and immunogenic compositions may be administered either prior to or following surgical removal of primary tumors and/or treatment such as administration of radiotherapy or conventional chemotherapeutic drugs. Administration may be by any suitable method, including administration by intravenous, intraperitoneal, intramuscular, subcutaneous, intranasal, intradermal, anal, vaginal, topical
25 and oral routes.

Within certain embodiments, immunotherapy may be active immunotherapy, in which treatment relies on the *in vivo* stimulation of the endogenous host

immune system to react against tumors with the administration of immune response-modifying agents (such as polypeptides and polynucleotides as provided herein).

Within other embodiments, immunotherapy may be passive immunotherapy, in which treatment involves the delivery of agents with established tumor-
5 immune reactivity (such as effector cells or antibodies) that can directly or indirectly mediate antitumor effects and does not necessarily depend on an intact host immune system. Examples of effector cells include T cells as discussed above, T lymphocytes (such as CD8⁺ cytotoxic T lymphocytes and CD4⁺ T-helper tumor-infiltrating lymphocytes), killer cells (such as Natural Killer cells and lymphokine-activated killer
10 cells), B cells and antigen-presenting cells (such as dendritic cells and macrophages) expressing a polypeptide provided herein. T cell receptors and antibody receptors specific for the polypeptides recited herein may be cloned, expressed and transferred into other vectors or effector cells for adoptive immunotherapy. The polypeptides provided herein may also be used to generate antibodies or anti-idiotypic antibodies (as described above
15 and in U.S. Patent No. 4,918,164) for passive immunotherapy.

Effector cells may generally be obtained in sufficient quantities for adoptive immunotherapy by growth *in vitro*, as described herein. Culture conditions for expanding single antigen-specific effector cells to several billion in number with retention of antigen recognition *in vivo* are well known in the art. Such *in vitro* culture conditions typically use
20 intermittent stimulation with antigen, often in the presence of cytokines (such as IL-2) and non-dividing feeder cells. As noted above, immunoreactive polypeptides as provided herein may be used to rapidly expand antigen-specific T cell cultures in order to generate a sufficient number of cells for immunotherapy. In particular, antigen-presenting cells, such as dendritic, macrophage, monocyte, fibroblast and/or B cells, may be pulsed with
25 immunoreactive polypeptides or transfected with one or more polynucleotides using standard techniques well known in the art. For example, antigen-presenting cells can be transfected with a polynucleotide having a promoter appropriate for increasing expression in a recombinant virus or other expression system. Cultured effector cells for use in therapy must be able to grow and distribute widely, and to survive long term *in vivo*.

Studies have shown that cultured effector cells can be induced to grow *in vivo* and to survive long term in substantial numbers by repeated stimulation with antigen supplemented with IL-2 (see, for example, Cheever *et al.*, *Immunological Reviews* 157:177, 1997).

5 Alternatively, a vector expressing a polypeptide recited herein may be introduced into antigen presenting cells taken from a patient and clonally propagated *ex vivo* for transplant back into the same patient. Transfected cells may be reintroduced into the patient using any means known in the art, preferably in sterile form by intravenous, intracavitory, intraperitoneal or intratumor administration.

10 Routes and frequency of administration of the therapeutic compositions described herein, as well as dosage, will vary from individual to individual, and may be readily established using standard techniques. In general, the pharmaceutical compositions and immunogenic compositions may be administered by injection (*e.g.*, intracutaneous, intramuscular, intravenous or subcutaneous), intranasally (*e.g.*, by aspiration) or orally.

15 Preferably, between 1 and 10 doses may be administered over a 52 week period. Preferably, 6 doses are administered, at intervals of 1 month, and booster vaccinations may be given periodically thereafter. Alternate protocols may be appropriate for individual patients. A suitable dose is an amount of a compound that, when administered as described above, is capable of promoting an anti-tumor immune response, and is at least 10-50% above the basal (*i.e.*, untreated) level. Such response can be monitored by measuring the anti-tumor antibodies in a patient or by vaccine-dependent generation of cytolytic effector cells capable of killing the patient's tumor cells *in vitro*. Such immunogenic compositions should also be capable of causing an immune response that leads to an improved clinical outcome (*e.g.*, more frequent remissions, complete or partial or longer disease-free survival) in treated patients as compared to non-treated patients. In general, for pharmaceutical compositions and immunogenic compositions comprising one or more polypeptides, the amount of each polypeptide present in a dose ranges from about 25 µg to 5 mg per kg of host. Suitable dose sizes will vary with the size of the patient, but will typically range from about 0.1 mL to about 5 mL.

In general, an appropriate dosage and treatment regimen provides the active compound(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit. Such a response can be monitored by establishing an improved clinical outcome (*e.g.*, more frequent remissions, complete or partial, or longer disease-free survival) in treated patients 5 as compared to non-treated patients. Increases in preexisting immune responses to a prostate-specific protein generally correlate with an improved clinical outcome. Such immune responses may generally be evaluated using standard proliferation, cytotoxicity or cytokine assays, which may be performed using samples obtained from a patient before and after treatment.

10 CANCER DETECTION AND DIAGNOSIS

In general, a cancer may be detected in a patient based on the presence of one or more prostate-specific proteins and/or polynucleotides encoding such proteins in a biological sample (for example, blood, sera, sputum urine and/or tumor biopsies) obtained from the patient. In other words, such proteins may be used as markers to indicate the 15 presence or absence of a cancer such as prostate cancer. In addition, such proteins may be useful for the detection of other cancers. The binding agents provided herein generally permit detection of the level of antigen that binds to the agent in the biological sample. Polynucleotide primers and probes may be used to detect the level of mRNA encoding a tumor protein, which is also indicative of the presence or absence of a cancer. In general, a 20 prostate-specific sequence should be present at a level that is at least three fold higher in prostate tissue than in other normal tissues.

There are a variety of assay formats known to those of ordinary skill in the art for using a binding agent to detect polypeptide markers in a sample. *See, e.g.*, Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In 25 general, the presence or absence of a cancer in a patient may be determined by (a) contacting a biological sample obtained from a patient with a binding agent; (b) detecting in the sample a level of polypeptide that binds to the binding agent; and (c) comparing the level of polypeptide with a predetermined cut-off value.

In a preferred embodiment, the assay involves the use of binding agent immobilized on a solid support to bind to and remove the polypeptide from the remainder of the sample. The bound polypeptide may then be detected using a detection reagent that contains a reporter group and specifically binds to the binding agent/polypeptide complex.

- 5 Such detection reagents may comprise, for example, a binding agent that specifically binds to the polypeptide or an antibody or other agent that specifically binds to the binding agent, such as an anti-immunoglobulin, protein G, protein A or a lectin. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized binding agent after incubation of the binding agent
10 with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding agent is indicative of the reactivity of the sample with the immobilized binding agent. Suitable polypeptides for use within such assays include full length prostate-specific proteins and portions thereof to which the binding agent binds, as described above.

- 15 The solid support may be any material known to those of ordinary skill in the art to which the tumor protein may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass, fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic
20 particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which
25 may be a direct linkage between the agent and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for a suitable amount of time. The contact time varies with temperature, but is typically between about 1

hour and about 1 day. In general, contacting a well of a plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about 10 µg, and preferably about 100 ng to about 1 µg, is sufficient to immobilize an adequate amount of binding agent.

5 Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group
10 on the support with an amine and an active hydrogen on the binding partner (*see, e.g.,* Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

In certain embodiments, the assay is a two-antibody sandwich assay. This assay may be performed by first contacting an antibody that has been immobilized on a solid support, commonly the well of a microtiter plate, with the sample, such that
15 polypeptides within the sample are allowed to bind to the immobilized antibody. Unbound sample is then removed from the immobilized polypeptide-antibody complexes and a detection reagent (preferably a second antibody capable of binding to a different site on the polypeptide) containing a reporter group is added. The amount of detection reagent that remains bound to the solid support is then determined using a method appropriate for the
20 specific reporter group.

More specifically, once the antibody is immobilized on the support as described above, the remaining protein binding sites on the support are typically blocked. Any suitable blocking agent known to those of ordinary skill in the art, such as bovine serum albumin or Tween 20TM (Sigma Chemical Co., St. Louis, MO). The immobilized
25 antibody is then incubated with the sample, and polypeptide is allowed to bind to the antibody. The sample may be diluted with a suitable diluent, such as phosphate-buffered saline (PBS) prior to incubation. In general, an appropriate contact time (*i.e.,* incubation time) is a period of time that is sufficient to detect the presence of polypeptide within a sample obtained from an individual with prostate cancer. Preferably, the contact time is

sufficient to achieve a level of binding that is at least about 95% of that achieved at equilibrium between bound and unbound polypeptide. Those of ordinary skill in the art will recognize that the time necessary to achieve equilibrium may be readily determined by assaying the level of binding that occurs over a period of time. At room temperature, an 5 incubation time of about 30 minutes is generally sufficient.

Unbound sample may then be removed by washing the solid support with an appropriate buffer, such as PBS containing 0.1% Tween 20TM. The second antibody, which contains a reporter group, may then be added to the solid support. Preferred reporter groups include those groups recited above.

10 The detection reagent is then incubated with the immobilized antibody-polypeptide complex for an amount of time sufficient to detect the bound polypeptide. An appropriate amount of time may generally be determined by assaying the level of binding that occurs over a period of time. Unbound detection reagent is then removed and bound detection reagent is detected using the reporter group. The method employed for detecting
15 the reporter group depends upon the nature of the reporter group. For radioactive groups, scintillation counting or autoradiographic methods are generally appropriate. Spectroscopic methods may be used to detect dyes, luminescent groups and fluorescent groups. Biotin may be detected using avidin, coupled to a different reporter group (commonly a radioactive or fluorescent group or an enzyme). Enzyme reporter groups may
20 generally be detected by the addition of substrate (generally for a specific period of time), followed by spectroscopic or other analysis of the reaction products.

To determine the presence or absence of a cancer, such as prostate cancer, the signal detected from the reporter group that remains bound to the solid support is generally compared to a signal that corresponds to a predetermined cut-off value. In one
25 preferred embodiment, the cut-off value for the detection of a cancer is the average mean signal obtained when the immobilized antibody is incubated with samples from patients without the cancer. In general, a sample generating a signal that is three standard deviations above the predetermined cut-off value is considered positive for the cancer. In an alternate preferred embodiment, the cut-off value is determined using a Receiver

Operator Curve, according to the method of Sackett *et al.*, *Clinical Epidemiology: A Basic Science for Clinical Medicine*, Little Brown and Co., 1985, p. 106-7. Briefly, in this embodiment, the cut-off value may be determined from a plot of pairs of true positive rates (*i.e.*, sensitivity) and false positive rates (100%-specificity) that correspond to each possible 5 cut-off value for the diagnostic test result. The cut-off value on the plot that is the closest to the upper left-hand corner (*i.e.*, the value that encloses the largest area) is the most accurate cut-off value, and a sample generating a signal that is higher than the cut-off value determined by this method may be considered positive. Alternatively, the cut-off value may be shifted to the left along the plot, to minimize the false positive rate, or to the right, 10 to minimize the false negative rate. In general, a sample generating a signal that is higher than the cut-off value determined by this method is considered positive for a cancer.

In a related embodiment, the assay is performed in a flow-through or strip test format, wherein the binding agent is immobilized on a membrane, such as nitrocellulose. In the flow-through test, polypeptides within the sample bind to the 15 immobilized binding agent as the sample passes through the membrane. A second, labeled binding agent then binds to the binding agent-polypeptide complex as a solution containing the second binding agent flows through the membrane. The detection of bound second binding agent may then be performed as described above. In the strip test format, one end of the membrane to which binding agent is bound is immersed in a solution containing the 20 sample. The sample migrates along the membrane through a region containing second binding agent and to the area of immobilized binding agent. Concentration of second binding agent at the area of immobilized antibody indicates the presence of a cancer. Typically, the concentration of second binding agent at that site generates a pattern, such as a line, that can be read visually. The absence of such a pattern indicates a negative result. 25 In general, the amount of binding agent immobilized on the membrane is selected to generate a visually discernible pattern when the biological sample contains a level of polypeptide that would be sufficient to generate a positive signal in the two-antibody sandwich assay, in the format discussed above. Preferred binding agents for use in such assays are antibodies and antigen-binding fragments thereof. Preferably, the amount of

antibody immobilized on the membrane ranges from about 25 ng to about 1 μ g, and more preferably from about 50 ng to about 500 ng. Such tests can typically be performed with a very small amount of biological sample.

Of course, numerous other assay protocols exist that are suitable for use
5 with the tumor proteins or binding agents of the present invention. The above descriptions are intended to be exemplary only. For example, it will be apparent to those of ordinary skill in the art that the above protocols may be readily modified to use prostate-specific polypeptides to detect antibodies that bind to such polypeptides in a biological sample. The detection of such prostate-specific protein specific antibodies may correlate with the
10 presence of a cancer.

A cancer may also, or alternatively, be detected based on the presence of T cells that specifically react with a prostate-specific protein in a biological sample. Within certain methods, a biological sample comprising CD4 $^{+}$ and/or CD8 $^{+}$ T cells isolated from a patient is incubated with a prostate-specific polypeptide, a polynucleotide encoding such a
15 polypeptide and/or an APC that expresses at least an immunogenic portion of such a polypeptide, and the presence or absence of specific activation of the T cells is detected. Suitable biological samples include, but are not limited to, isolated T cells. For example, T cells may be isolated from a patient by routine techniques (such as by Ficoll/Hypaque density gradient centrifugation of peripheral blood lymphocytes). T cells may be incubated
20 *in vitro* for 2-9 days (typically 4 days) at 37°C with polypeptide (*e.g.*, 5 - 25 μ g/ml). It may be desirable to incubate another aliquot of a T cell sample in the absence of prostate-specific polypeptide to serve as a control. For CD4 $^{+}$ T cells, activation is preferably detected by evaluating proliferation of the T cells. For CD8 $^{+}$ T cells, activation is preferably detected by evaluating cytolytic activity. A level of proliferation that is at least
25 two fold greater and/or a level of cytolytic activity that is at least 20% greater than in disease-free patients indicates the presence of a cancer in the patient.

As noted above, a cancer may also, or alternatively, be detected based on the level of mRNA encoding a prostate-specific protein in a biological sample. For example, at least two oligonucleotide primers may be employed in a polymerase chain reaction

(PCR) based assay to amplify a portion of a prostate-specific cDNA derived from a biological sample, wherein at least one of the oligonucleotide primers is specific for (*i.e.*, hybridizes to) a polynucleotide encoding the prostate-specific protein. The amplified cDNA is then separated and detected using techniques well known in the art, such as gel electrophoresis. Similarly, oligonucleotide probes that specifically hybridize to a polynucleotide encoding a prostate-specific protein may be used in a hybridization assay to detect the presence of polynucleotide encoding the tumor protein in a biological sample.

To permit hybridization under assay conditions, oligonucleotide primers and probes should comprise an oligonucleotide sequence that has at least about 60%, preferably at least about 75% and more preferably at least about 90%, identity to a portion of a polynucleotide encoding a prostate-specific protein that is at least 10 nucleotides, and preferably at least 20 nucleotides, in length. Preferably, oligonucleotide primers and/or probes hybridize to a polynucleotide encoding a polypeptide described herein under moderately stringent conditions, as defined above. Oligonucleotide primers and/or probes which may be usefully employed in the diagnostic methods described herein preferably are at least 10-40 nucleotides in length. In a preferred embodiment, the oligonucleotide primers comprise at least 10 contiguous nucleotides, more preferably at least 15 contiguous nucleotides, of a DNA molecule having a sequence recited in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777 and 789. Techniques for both PCR based assays and hybridization assays are well known in the art (*see, for example, Mullis et al., Cold Spring Harbor Symp. Quant. Biol., 51:263, 1987; Erlich ed., PCR Technology, Stockton Press, NY, 1989.*)

One preferred assay employs RT-PCR, in which PCR is applied in conjunction with reverse transcription. Typically, RNA is extracted from a biological sample, such as biopsy tissue, and is reverse transcribed to produce cDNA molecules. PCR amplification using at least one specific primer generates a cDNA molecule, which may be separated and visualized using, for example, gel electrophoresis. Amplification may be performed on biological samples taken from a test patient and from an individual who is

not afflicted with a cancer. The amplification reaction may be performed on several dilutions of cDNA spanning two orders of magnitude. A two-fold or greater increase in expression in several dilutions of the test patient sample as compared to the same dilutions of the non-cancerous sample is typically considered positive.

5 In another embodiment, the compositions described herein may be used as markers for the progression of cancer. In this embodiment, assays as described above for the diagnosis of a cancer may be performed over time, and the change in the level of reactive polypeptide(s) or polynucleotide(s) evaluated. For example, the assays may be performed every 24-72 hours for a period of 6 months to 1 year, and thereafter performed
10 as needed. In general, a cancer is progressing in those patients in whom the level of polypeptide or polynucleotide detected increases over time. In contrast, the cancer is not progressing when the level of reactive polypeptide or polynucleotide either remains constant or decreases with time.

Certain *in vivo* diagnostic assays may be performed directly on a tumor.
15 One such assay involves contacting tumor cells with a binding agent. The bound binding agent may then be detected directly or indirectly via a reporter group. Such binding agents may also be used in histological applications. Alternatively, polynucleotide probes may be used within such applications.

As noted above, to improve sensitivity, multiple prostate-specific protein
20 markers may be assayed within a given sample. It will be apparent that binding agents specific for different proteins provided herein may be combined within a single assay. Further, multiple primers or probes may be used concurrently. The selection of tumor protein markers may be based on routine experiments to determine combinations that results in optimal sensitivity. In addition, or alternatively, assays for tumor proteins
25 provided herein may be combined with assays for other known tumor antigens.

DIAGNOSTIC KITS

The present invention further provides kits for use within any of the above diagnostic methods. Such kits typically comprise two or more components necessary for

performing a diagnostic assay. Components may be compounds, reagents, containers and/or equipment. For example, one container within a kit may contain a monoclonal antibody or fragment thereof that specifically binds to a prostate-specific protein. Such antibodies or fragments may be provided attached to a support material, as described above. One or more additional containers may enclose elements, such as reagents or buffers, to be used in the assay. Such kits may also, or alternatively, contain a detection reagent as described above that contains a reporter group suitable for direct or indirect detection of antibody binding.

Alternatively, a kit may be designed to detect the level of mRNA encoding a prostate-specific protein in a biological sample. Such kits generally comprise at least one oligonucleotide probe or primer, as described above, that hybridizes to a polynucleotide encoding a prostate-specific protein. Such an oligonucleotide may be used, for example, within a PCR or hybridization assay. Additional components that may be present within such kits include a second oligonucleotide and/or a diagnostic reagent or container to facilitate the detection of a polynucleotide encoding a prostate-specific protein.

The following Examples are offered by way of illustration and not by way of limitation.

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EXAMPLE 1

ISOLATION AND CHARACTERIZATION OF PROSTATE-SPECIFIC POLYPEPTIDES

This Example describes the isolation of certain prostate-specific
5 polypeptides from a prostate tumor cDNA library.

A human prostate tumor cDNA expression library was constructed from prostate tumor poly A⁺ RNA using a Superscript Plasmid System for cDNA Synthesis and Plasmid Cloning kit (BRL Life Technologies, Gaithersburg, MD 20897) following the manufacturer's protocol. Specifically, prostate tumor tissues were homogenized with 10 polytron (Kinematica, Switzerland) and total RNA was extracted using Trizol reagent (BRL Life Technologies) as directed by the manufacturer. The poly A⁺ RNA was then purified using a Qiagen oligotex spin column mRNA purification kit (Qiagen, Santa Clarita, CA 91355) according to the manufacturer's protocol. First-strand cDNA was synthesized using the NotI/Oligo-dT18 primer. Double-stranded cDNA was synthesized, 15 ligated with EcoRI/BAXI adaptors (Invitrogen, San Diego, CA) and digested with NotI. Following size fractionation with Chroma Spin-1000 columns (Clontech, Palo Alto, CA), the cDNA was ligated into the EcoRI/NotI site of pCDNA3.1 (Invitrogen) and transformed into ElectroMax *E. coli* DH10B cells (BRL Life Technologies) by electroporation.

Using the same procedure, a normal human pancreas cDNA expression 20 library was prepared from a pool of six tissue specimens (Clontech). The cDNA libraries were characterized by determining the number of independent colonies, the percentage of clones that carried insert, the average insert size and by sequence analysis. The prostate tumor library contained 1.64×10^7 independent colonies, with 70% of clones having an insert and the average insert size being 1745 base pairs. The normal pancreas cDNA 25 library contained 3.3×10^6 independent colonies, with 69% of clones having inserts and the average insert size being 1120 base pairs. For both libraries, sequence analysis showed that the majority of clones had a full length cDNA sequence and were synthesized from mRNA, with minimal rRNA and mitochondrial DNA contamination.

cDNA library subtraction was performed using the above prostate tumor and normal pancreas cDNA libraries, as described by Hara *et al.* (*Blood*, 84:189-199, 1994) with some modifications. Specifically, a prostate tumor-specific subtracted cDNA library was generated as follows. Normal pancreas cDNA library (70 µg) was digested with 5 EcoRI, NotI, and SfI, followed by a filling-in reaction with DNA polymerase Klenow fragment. After phenol-chloroform extraction and ethanol precipitation, the DNA was dissolved in 100 µl of H₂O, heat-denatured and mixed with 100 µl (100 µg) of Photoprobe biotin (Vector Laboratories, Burlingame, CA). As recommended by the manufacturer, the resulting mixture was irradiated with a 270 W sunlamp on ice for 20 minutes. Additional 10 Photoprobe biotin (50 µl) was added and the biotinylation reaction was repeated. After extraction with butanol five times, the DNA was ethanol-precipitated and dissolved in 23 µl H₂O to form the driver DNA.

To form the tracer DNA, 10 µg prostate tumor cDNA library was digested with BamHI and XhoI, phenol chloroform extracted and passed through Chroma spin-400 15 columns (Clontech). Following ethanol precipitation, the tracer DNA was dissolved in 5 µl H₂O. Tracer DNA was mixed with 15 µl driver DNA and 20 µl of 2 x hybridization buffer (1.5 M NaCl/10 mM EDTA/50 mM HEPES pH 7.5/0.2% sodium dodecyl sulfate), overlaid with mineral oil, and heat-denatured completely. The sample was immediately transferred into a 68 °C water bath and incubated for 20 hours (long hybridization [LH]). The reaction 20 mixture was then subjected to a streptavidin treatment followed by phenol/chloroform extraction. This process was repeated three more times. Subtracted DNA was precipitated, dissolved in 12 µl H₂O, mixed with 8 µl driver DNA and 20 µl of 2 x hybridization buffer, and subjected to a hybridization at 68 °C for 2 hours (short hybridization [SH]). After removal of biotinylated double-stranded DNA, subtracted cDNA was ligated into 25 BamHI/XhoI site of chloramphenicol resistant pBCSK⁺ (Stratagene, La Jolla, CA 92037) and transformed into ElectroMax *E. coli* DH10B cells by electroporation to generate a prostate tumor specific subtracted cDNA library (referred to as “prostate subtraction 1”).

To analyze the subtracted cDNA library, plasmid DNA was prepared from 100 independent clones, randomly picked from the subtracted prostate tumor specific

library and grouped based on insert size. Representative cDNA clones were further characterized by DNA sequencing with a Perkin Elmer/Applied Biosystems Division Automated Sequencer Model 373A (Foster City, CA). Six cDNA clones, hereinafter referred to as F1-13, F1-12, F1-16, H1-1, H1-9 and H1-4, were shown to be abundant in
5 the subtracted prostate-specific cDNA library. The determined 3' and 5' cDNA sequences for F1-12 are provided in SEQ ID NO: 2 and 3, respectively, with determined 3' cDNA sequences for F1-13, F1-16, H1-1, H1-9 and H1-4 being provided in SEQ ID NO: 1 and 4-7, respectively.

The cDNA sequences for the isolated clones were compared to known
10 sequences in the gene bank using the EMBL and GenBank databases (release 96). Four of the prostate tumor cDNA clones, F1-13, F1-16, H1-1, and H1-4, were determined to encode the following previously identified proteins: prostate specific antigen (PSA), human glandular kallikrein, human tumor expression enhanced gene, and mitochondria cytochrome C oxidase subunit II. H1-9 was found to be identical to a previously identified
15 human autonomously replicating sequence. No significant homologies to the cDNA sequence for F1-12 were found.

Subsequent studies led to the isolation of a full-length cDNA sequence for F1-12 (also referred to as P504S). This sequence is provided in SEQ ID NO: 107, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 108. cDNA
20 splice variants of P504S are provided in SEQ ID NO: 600-605.

To clone less abundant prostate tumor specific genes, cDNA library subtraction was performed by subtracting the prostate tumor cDNA library described above with the normal pancreas cDNA library and with the three most abundant genes in the previously subtracted prostate tumor specific cDNA library: human glandular kallikrein,
25 prostate specific antigen (PSA), and mitochondria cytochrome C oxidase subunit II. Specifically, 1 µg each of human glandular kallikrein, PSA and mitochondria cytochrome C oxidase subunit II cDNAs in pCDNA3.1 were added to the driver DNA and subtraction was performed as described above to provide a second subtracted cDNA library hereinafter referred to as the "subtracted prostate tumor specific cDNA library with spike".

Twenty-two cDNA clones were isolated from the subtracted prostate tumor specific cDNA library with spike. The determined 3' and 5' cDNA sequences for the clones referred to as J1-17, L1-12, N1-1862, J1-13, J1-19, J1-25, J1-24, K1-58, K1-63, L1-4 and L1-14 are provided in SEQ ID NOS: 8-9, 10-11, 12-13, 14-15, 16-17, 18-19, 20-21,
5 22-23, 24-25, 26-27 and 28-29, respectively. The determined 3' cDNA sequences for the clones referred to as J1-12, J1-16, J1-21, K1-48, K1-55, L1-2, L1-6, N1-1858, N1-1860, N1-1861, N1-1864 are provided in SEQ ID NOS: 30-40, respectively. Comparison of these sequences with those in the gene bank as described above, revealed no significant homologies to three of the five most abundant DNA species, (J1-17, L1-12 and N1-1862;
10 SEQ ID NOS: 8-9, 10-11 and 12-13, respectively). Of the remaining two most abundant species, one (J1-12; SEQ ID NO:30) was found to be identical to the previously identified human pulmonary surfactant-associated protein, and the other (K1-48; SEQ ID NO:33) was determined to have some homology to *R. norvegicus* mRNA for 2-arylpropionyl-CoA epimerase. Of the 17 less abundant cDNA clones isolated from the subtracted prostate
15 tumor specific cDNA library with spike, four (J1-16, K1-55, L1-6 and N1-1864; SEQ ID NOS:31, 34, 36 and 40, respectively) were found to be identical to previously identified sequences, two (J1-21 and N1-1860; SEQ ID NOS: 32 and 38, respectively) were found to show some homology to non-human sequences, and two (L1-2 and N1-1861; SEQ ID NOS: 35 and 39, respectively) were found to show some homology to known human
20 sequences. No significant homologies were found to the polypeptides J1-13, J1-19, J1-24, J1-25, K1-58, K1-63, L1-4, L1-14 (SEQ ID NOS: 14-15, 16-17, 20-21, 18-19, 22-23, 24-25, 26-27, 28-29, respectively).

Subsequent studies led to the isolation of full length cDNA sequences for J1-17, L1-12 and N1-1862 (SEQ ID NOS: 109-111, respectively). The corresponding
25 predicted amino acid sequences are provided in SEQ ID NOS: 112-114. L1-12 is also referred to as P501S. A cDNA splice variant of P501S is provided in SEQ ID NO: 606.

In a further experiment, four additional clones were identified by subtracting a prostate tumor cDNA library with normal prostate cDNA prepared from a pool of three normal prostate poly A+ RNA (referred to as "prostate subtraction 2"). The determined

cDNA sequences for these clones, hereinafter referred to as U1-3064, U1-3065, V1-3692 and 1A-3905, are provided in SEQ ID NO: 69-72, respectively. Comparison of the determined sequences with those in the gene bank revealed no significant homologies to U1-3065.

5 A second subtraction with spike (referred to as "prostate subtraction spike 2") was performed by subtracting a prostate tumor specific cDNA library with spike with normal pancreas cDNA library and further spiked with PSA, J1-17, pulmonary surfactant-associated protein, mitochondrial DNA, cytochrome c oxidase subunit II, N1-1862, autonomously replicating sequence, L1-12 and tumor expression enhanced gene. Four
10 additional clones, hereinafter referred to as V1-3686, R1-2330, 1B-3976 and V1-3679, were isolated. The determined cDNA sequences for these clones are provided in SEQ ID NO:73-76, respectively. Comparison of these sequences with those in the gene bank revealed no significant homologies to V1-3686 and R1-2330.

Further analysis of the three prostate subtractions described above (prostate subtraction 2, subtracted prostate tumor specific cDNA library with spike, and prostate subtraction spike 2) resulted in the identification of sixteen additional clones, referred to as 1G-4736, 1G-4738, 1G-4741, 1G-4744, 1G-4734, 1H-4774, 1H-4781, 1H-4785, 1H-4787, 1H-4796, 1I-4810, 1I-4811, 1J-4876, 1K-4884 and 1K-4896. The determined cDNA sequences for these clones are provided in SEQ ID NOS: 77-92, respectively. Comparison
15 of these sequences with those in the gene bank as described above, revealed no significant homologies to 1G-4741, 1G-4734, 1I-4807, 1J-4876 and 1K-4896 (SEQ ID NOS: 79, 81, 87, 90 and 92, respectively). Further analysis of the isolated clones led to the determination of extended cDNA sequences for 1G-4736, 1G-4738, 1G-4741, 1G-4744, 1H-4774, 1H-4781, 1H-4785, 1H-4787, 1H-4796, 1I-4807, 1J-4876, 1K-4884 and 1K-
20 4896, provided in SEQ ID NOS: 179-188 and 191-193, respectively, and to the determination of additional partial cDNA sequences for 1I-4810 and 1I-4811, provided in SEQ ID NOS: 189 and 190, respectively.

Additional studies with prostate subtraction spike 2 resulted in the isolation of three more clones. Their sequences were determined as described above and compared

to the most recent GenBank. All three clones were found to have homology to known genes, which are Cysteine-rich protein, KIAA0242, and KIAA0280 (SEQ ID NO: 317, 319, and 320, respectively). Further analysis of these clones by Synteni microarray (Synteni, Palo Alto, CA) demonstrated that all three clones were over-expressed in most 5 prostate tumors and prostate BPH, as well as in the majority of normal prostate tissues tested, but low expression in all other normal tissues.

An additional subtraction was performed by subtracting a normal prostate cDNA library with normal pancreas cDNA (referred to as “prostate subtraction 3”). This led to the identification of six additional clones referred to as 1G-4761, 1G-4762, 1H-4766, 10 1H-4770, 1H-4771 and 1H-4772 (SEQ ID NOS: 93-98). Comparison of these sequences with those in the gene bank revealed no significant homologies to 1G-4761 and 1H-4771 (SEQ ID NOS: 93 and 97, respectively). Further analysis of the isolated clones led to the determination of extended cDNA sequences for 1G-4761, 1G-4762, 1H-4766 and 1H-4772 provided in SEQ ID NOS: 194-196 and 199, respectively, and to the determination of 15 additional partial cDNA sequences for 1H-4770 and 1H-4771, provided in SEQ ID NOS: 197 and 198, respectively.

Subtraction of a prostate tumor cDNA library, prepared from a pool of polyA+ RNA from three prostate cancer patients, with a normal pancreas cDNA library (prostate subtraction 4) led to the identification of eight clones, referred to as 1D-4297, 1D- 20 4309, 1D.1-4278, 1D-4288, 1D-4283, 1D-4304, 1D-4296 and 1D-4280 (SEQ ID NOS: 99-107). These sequences were compared to those in the gene bank as described above. No significant homologies were found to 1D-4283 and 1D-4304 (SEQ ID NOS: 103 and 104, respectively). Further analysis of the isolated clones led to the determination of extended cDNA sequences for 1D-4309, 1D.1-4278, 1D-4288, 1D-4283, 1D-4304, 1D-4296 and 1D- 25 4280, provided in SEQ ID NOS: 200-206, respectively.

cDNA clones isolated in prostate subtraction 1 and prostate subtraction 2, described above, were colony PCR amplified and their mRNA expression levels in prostate tumor, normal prostate and in various other normal tissues were determined using microarray technology (Synteni, Palo Alto, CA). Briefly, the PCR amplification products

were dotted onto slides in an array format, with each product occupying a unique location in the array. mRNA was extracted from the tissue sample to be tested, reverse transcribed, and fluorescent-labeled cDNA probes were generated. The microarrays were probed with the labeled cDNA probes, the slides scanned and fluorescence intensity was measured.

- 5 This intensity correlates with the hybridization intensity. Two clones (referred to as P509S and P510S) were found to be over-expressed in prostate tumor and normal prostate and expressed at low levels in all other normal tissues tested (liver, pancreas, skin, bone marrow, brain, breast, adrenal gland, bladder, testes, salivary gland, large intestine, kidney, ovary, lung, spinal cord, skeletal muscle and colon). The determined cDNA sequences for
10 P509S and P510S are provided in SEQ ID NO: 223 and 224, respectively. Comparison of these sequences with those in the gene bank as described above, revealed some homology to previously identified ESTs.

Additional studies led to the isolation of the full-length cDNA sequence for P509S. This sequence is provided in SEQ ID NO: 332, with the corresponding predicted
15 amino acid sequence being provided in SEQ ID NO: 339. Two variant full-length cDNA sequences for P510S are provided in SEQ ID NO: 535 and 536, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 537 and 538, respectively. Additional splice variants of P510S are provided in SEQ ID NO: 598 and 599.

The determined cDNA sequences for additional prostate-specific clones
20 isolated during characterization of prostate specific cDNA libraries are provided in SEQ ID NO: 618-689, 691-697 and 709-772. Comparison of these sequences with those in the public databases revealed no significant homologies to any of these sequences.

EXAMPLE 2

25 DETERMINATION OF TISSUE SPECIFICITY OF PROSTATE-SPECIFIC POLYPEPTIDES

Using gene specific primers, mRNA expression levels for the representative prostate-specific polypeptides F1-16, H1-1, J1-17 (also referred to as P502S), L1-12 (also

referred to as P501S), F1-12 (also referred to as P504S) and N1-1862 (also referred to as P503S) were examined in a variety of normal and tumor tissues using RT-PCR.

Briefly, total RNA was extracted from a variety of normal and tumor tissues using Trizol reagent as described above. First strand synthesis was carried out using 1-2 µg of total RNA with SuperScript II reverse transcriptase (BRL Life Technologies) at 42 °C for one hour. The cDNA was then amplified by PCR with gene-specific primers. To ensure the semi-quantitative nature of the RT-PCR, β-actin was used as an internal control for each of the tissues examined. First, serial dilutions of the first strand cDNAs were prepared and RT-PCR assays were performed using β-actin specific primers. A dilution was then chosen that enabled the linear range amplification of the β-actin template and which was sensitive enough to reflect the differences in the initial copy numbers. Using these conditions, the β-actin levels were determined for each reverse transcription reaction from each tissue. DNA contamination was minimized by DNase treatment and by assuring a negative PCR result when using first strand cDNA that was prepared without adding reverse transcriptase.

mRNA Expression levels were examined in four different types of tumor tissue (prostate tumor from 2 patients, breast tumor from 3 patients, colon tumor, lung tumor), and sixteen different normal tissues, including prostate, colon, kidney, liver, lung, ovary, pancreas, skeletal muscle, skin, stomach, testes, bone marrow and brain. F1-16 was found to be expressed at high levels in prostate tumor tissue, colon tumor and normal prostate, and at lower levels in normal liver, skin and testes, with expression being undetectable in the other tissues examined. H1-1 was found to be expressed at high levels in prostate tumor, lung tumor, breast tumor, normal prostate, normal colon and normal brain, at much lower levels in normal lung, pancreas, skeletal muscle, skin, small intestine, bone marrow, and was not detected in the other tissues tested. J1-17 (P502S) and L1-12 (P501S) appear to be specifically over-expressed in prostate, with both genes being expressed at high levels in prostate tumor and normal prostate but at low to undetectable levels in all the other tissues examined. N1-1862 (P503S) was found to be over-expressed in 60% of prostate tumors and detectable in normal colon and kidney. The RT-PCR results

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thus indicate that F1-16, H1-1, J1-17 (P502S), N1-1862 (P503S) and L1-12 (P501S) are either prostate specific or are expressed at significantly elevated levels in prostate.

Further RT-PCR studies showed that F1-12 (P504S) is over-expressed in 60% of prostate tumors, detectable in normal kidney but not detectable in all other tissues tested. Similarly, R1-2330 was shown to be over-expressed in 40% of prostate tumors, detectable in normal kidney and liver, but not detectable in all other tissues tested. U1-3064 was found to be over-expressed in 60% of prostate tumors, and also expressed in breast and colon tumors, but was not detectable in normal tissues.

RT-PCR characterization of R1-2330, U1-3064 and 1D-4279 showed that 10 these three antigens are over-expressed in prostate and/or prostate tumors.

Northern analysis with four prostate tumors, two normal prostate samples, two BPH prostates, and normal colon, kidney, liver, lung, pancreas, skeletal muscle, brain, stomach, testes, small intestine and bone marrow, showed that L1-12 (P501S) is over-expressed in prostate tumors and normal prostate, while being undetectable in other normal 15 tissues tested. J1-17 (P502S) was detected in two prostate tumors and not in the other tissues tested. N1-1862 (P503S) was found to be over-expressed in three prostate tumors and to be expressed in normal prostate, colon and kidney, but not in other tissues tested. F1-12 (P504S) was found to be highly expressed in two prostate tumors and to be undetectable in all other tissues tested.

20 The microarray technology described above was used to determine the expression levels of representative antigens described herein in prostate tumor, breast tumor and the following normal tissues: prostate, liver, pancreas, skin, bone marrow, brain, breast, adrenal gland, bladder, testes, salivary gland, large intestine, kidney, ovary, lung, spinal cord, skeletal muscle and colon. L1-12 (P501S) was found to be over-expressed in normal prostate and prostate tumor, with some expression being detected in 25 normal skeletal muscle. Both J1-12 and F1-12 (P504S) were found to be over-expressed in prostate tumor, with expression being lower or undetectable in all other tissues tested. N1-1862 (P503S) was found to be expressed at high levels in prostate tumor and normal prostate, and at low levels in normal large intestine and normal colon, with expression

being undetectable in all other tissues tested. R1-2330 was found to be over-expressed in prostate tumor and normal prostate, and to be expressed at lower levels in all other tissues tested. 1D-4279 was found to be over-expressed in prostate tumor and normal prostate, expressed at lower levels in normal spinal cord, and to be undetectable in all other tissues
5 tested.

Further microarray analysis to specifically address the extent to which P501S (SEQ ID NO: 110) was expressed in breast tumor revealed moderate over-expression not only in breast tumor, but also in metastatic breast tumor (2/31), with negligible to low expression in normal tissues. This data suggests that P501S may be over-
10 expressed in various breast tumors as well as in prostate tumors.

The expression levels of 32 ESTs (expressed sequence tags) described by Vasmatzis *et al.* (*Proc. Natl. Acad. Sci. USA* 95:300-304, 1998) in a variety of tumor and normal tissues were examined by microarray technology as described above. Two of these clones (referred to as P1000C and P1001C) were found to be over-expressed in prostate
15 tumor and normal prostate, and expressed at low to undetectable levels in all other tissues tested (normal aorta, thymus, resting and activated PBMC, epithelial cells, spinal cord, adrenal gland, fetal tissues, skin, salivary gland, large intestine, bone marrow, liver, lung, dendritic cells, stomach, lymph nodes, brain, heart, small intestine, skeletal muscle, colon and kidney. The determined cDNA sequences for P1000C and P1001C are provided in
20 SEQ ID NO: 384 and 472, respectively. The sequence of P1001C was found to show some homology to the previously isolated Human mRNA for JM27 protein. No significant homologies were found to the sequence of P1000C.

The expression of the polypeptide encoded by the full length cDNA sequence for F1-12 (also referred to as P504S; SEQ ID NO: 108) was investigated by
25 immunohistochemical analysis. Rabbit-anti-P504S polyclonal antibodies were generated against the full length P504S protein by standard techniques. Subsequent isolation and characterization of the polyclonal antibodies were also performed by techniques well known in the art. Immunohistochemical analysis showed that the P504S polypeptide was expressed in 100% of prostate carcinoma samples tested (n=5).

The rabbit-anti-P504S polyclonal antibody did not appear to label benign prostate cells with the same cytoplasmic granular staining, but rather with light nuclear staining. Analysis of normal tissues revealed that the encoded polypeptide was found to be expressed in some, but not all normal human tissues. Positive cytoplasmic staining with 5 rabbit-anti-P504S polyclonal antibody was found in normal human kidney, liver, brain, colon and lung-associated macrophages, whereas heart and bone marrow were negative.

This data indicates that the P504S polypeptide is present in prostate cancer tissues, and that there are qualitative and quantitative differences in the staining between benign prostatic hyperplasia tissues and prostate cancer tissues, suggesting that this 10 polypeptide may be detected selectively in prostate tumors and therefore be useful in the diagnosis of prostate cancer.

EXAMPLE 3

ISOLATION AND CHARACTERIZATION OF PROSTATE-SPECIFIC 15 POLYPEPTIDES BY PCR-BASED SUBTRACTION

A cDNA subtraction library, containing cDNA from normal prostate subtracted with ten other normal tissue cDNAs (brain, heart, kidney, liver, lung, ovary, placenta, skeletal muscle, spleen and thymus) and then submitted to a first round of PCR 20 amplification, was purchased from Clontech. This library was subjected to a second round of PCR amplification, following the manufacturer's protocol. The resulting cDNA fragments were subcloned into the vector pT7 Blue T-vector (Novagen, Madison, WI) and transformed into XL-1 Blue MRF' *E. coli* (Stratagene). DNA was isolated from independent clones and sequenced using a Perkin Elmer/Applied Biosystems Division 25 Automated Sequencer Model 373A.

Fifty-nine positive clones were sequenced. Comparison of the DNA sequences of these clones with those in the gene bank, as described above, revealed no significant homologies to 25 of these clones, hereinafter referred to as P5, P8, P9, P18, P20, P30, P34, P36, P38, P39, P42, P49, P50, P53, P55, P60, P64, P65, P73, P75, P76, P79

and P84. The determined cDNA sequences for these clones are provided in SEQ ID NO: 41-45, 47-52 and 54-65, respectively. P29, P47, P68, P80 and P82 (SEQ ID NO: 46, 53 and 66-68, respectively) were found to show some degree of homology to previously identified DNA sequences. To the best of the inventors' knowledge, none of these 5 sequences have been previously shown to be present in prostate.

Further studies employing the sequence of SEQ ID NO: 67 as a probe in standard full-length cloning methods, resulted in the isolation of three cDNA sequences which appear to be splice variants of P80 (also known as P704P). These sequences are provided in SEQ ID NO: 699-701.

10 Further studies using the PCR-based methodology described above resulted in the isolation of more than 180 additional clones, of which 23 clones were found to show no significant homologies to known sequences. The determined cDNA sequences for these clones are provided in SEQ ID NO: 115-123, 127, 131, 137, 145, 147-151, 153, 156-158 and 160. Twenty-three clones (SEQ ID NO: 124-126, 128-130, 132-136, 138-144, 146, 15 152, 154, 155 and 159) were found to show some homology to previously identified ESTs. An additional ten clones (SEQ ID NO: 161-170) were found to have some degree of homology to known genes. Larger cDNA clones containing the P20 sequence represent splice variants of a gene referred to as P703P. The determined DNA sequence for the variants referred to as DE1, DE13 and DE14 are provided in SEQ ID NOS: 171, 175 and 20 177, respectively, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 172, 176 and 178, respectively. The determined cDNA sequence for an extended spliced form of P703 is provided in SEQ ID NO: 225. The DNA sequences for the splice variants referred to as DE2 and DE6 are provided in SEQ ID NOS: 173 and 174, respectively.

25 mRNA Expression levels for representative clones in tumor tissues (prostate (n=5), breast (n=2), colon and lung) normal tissues (prostate (n=5), colon, kidney, liver, lung (n=2), ovary (n=2), skeletal muscle, skin, stomach, small intestine and brain), and activated and non-activated PBMC was determined by RT-PCR as described above. Expression was examined in one sample of each tissue type unless otherwise indicated.

P9 was found to be highly expressed in normal prostate and prostate tumor compared to all normal tissues tested except for normal colon which showed comparable expression. P20, a portion of the P703P gene, was found to be highly expressed in normal prostate and prostate tumor, compared to all twelve normal tissues tested. A modest increase in expression of P20 in breast tumor (n=2), colon tumor and lung tumor was seen compared to all normal tissues except lung (1 of 2). Increased expression of P18 was found in normal prostate, prostate tumor and breast tumor compared to other normal tissues except lung and stomach. A modest increase in expression of P5 was observed in normal prostate compared to most other normal tissues. However, some elevated expression was seen in normal lung and PBMC. Elevated expression of P5 was also observed in prostate tumors (2 of 5), breast tumor and one lung tumor sample. For P30, similar expression levels were seen in normal prostate and prostate tumor, compared to six of twelve other normal tissues tested. Increased expression was seen in breast tumors, one lung tumor sample and one colon tumor sample, and also in normal PBMC. P29 was found to be over-expressed in prostate tumor (5 of 5) and normal prostate (5 of 5) compared to the majority of normal tissues. However, substantial expression of P29 was observed in normal colon and normal lung (2 of 2). P80 was found to be over-expressed in prostate tumor (5 of 5) and normal prostate (5 of 5) compared to all other normal tissues tested, with increased expression also being seen in colon tumor.

Further studies resulted in the isolation of twelve additional clones, hereinafter referred to as 10-d8, 10-h10, 11-c8, 7-g6, 8-b5, 8-b6, 8-d4, 8-d9, 8-g3, 8-h11, 9-f12 and 9-f3. The determined DNA sequences for 10-d8, 10-h10, 11-c8, 8-d4, 8-d9, 8-h11, 9-f12 and 9-f3 are provided in SEQ ID NO: 207, 208, 209, 216, 217, 220, 221 and 222, respectively. The determined forward and reverse DNA sequences for 7-g6, 8-b5, 8-b6 and 8-g3 are provided in SEQ ID NO: 210 and 211; 212 and 213; 214 and 215; and 218 and 219, respectively. Comparison of these sequences with those in the gene bank revealed no significant homologies to the sequence of 9-f3. The clones 10-d8, 11-c8 and 8-h11 were found to show some homology to previously isolated ESTs, while 10-h10, 8-b5, 8-b6, 8-d4, 8-d9, 8-g3 and 9-f12 were found to show some homology to previously identified genes.

Further characterization of 7-G6 and 8-G3 showed identity to the known genes PAP and PSA, respectively.

mRNA expression levels for these clones were determined using the micro-array technology described above. The clones 7-G6, 8-G3, 8-B5, 8-B6, 8-D4, 8-D9, 9-F3, 5 9-F12, 9-H3, 10-A2, 10-A4, 11-C9 and 11-F2 were found to be over-expressed in prostate tumor and normal prostate, with expression in other tissues tested being low or undetectable. Increased expression of 8-F11 was seen in prostate tumor and normal prostate, bladder, skeletal muscle and colon. Increased expression of 10-H10 was seen in prostate tumor and normal prostate, bladder, lung, colon, brain and large intestine. 10 Increased expression of 9-B1 was seen in prostate tumor, breast tumor, and normal prostate, salivary gland, large intestine and skin, with increased expression of 11-C8 being seen in prostate tumor, and normal prostate and large intestine.

An additional cDNA fragment derived from the PCR-based normal prostate subtraction, described above, was found to be prostate specific by both micro-array 15 technology and RT-PCR. The determined cDNA sequence of this clone (referred to as 9-A11) is provided in SEQ ID NO: 226. Comparison of this sequence with those in the public databases revealed 99% identity to the known gene HOXB13.

Further studies led to the isolation of the clones 8-C6 and 8-H7. The determined cDNA sequences for these clones are provided in SEQ ID NO: 227 and 228, 20 respectively. These sequences were found to show some homology to previously isolated ESTs.

PCR and hybridization-based methodologies were employed to obtain longer cDNA sequences for clone P20 (also referred to as P703P), yielding three additional cDNA fragments that progressively extend the 5' end of the gene. These fragments, 25 referred to as P703PDE5, P703P6.26, and P703PX-23 (SEQ ID NO: 326, 328 and 330, with the predicted corresponding amino acid sequences being provided in SEQ ID NO: 327, 329 and 331, respectively) contain additional 5' sequence. P703PDE5 was recovered by screening of a cDNA library (#141-26) with a portion of P703P as a probe. P703P6.26 was recovered from a mixture of three prostate tumor cDNAs and P703PX_23 was

recovered from cDNA library (#438-48). Together, the additional sequences include all of the putative mature serine protease along with part of the putative signal sequence. The full-length cDNA sequence for P703P is provided in SEQ ID NO: 524, with the corresponding amino acid sequence being provided in SEQ ID NO: 525.

5 P703P was found to show some homology to previously identified proteases, such as thrombin. The thrombin receptor has been shown to be preferentially expressed in highly metastatic breast carcinoma cells and breast carcinoma biopsy samples. Introduction of thrombin receptor antisense cDNA has been shown to inhibit the invasion 10 of metastatic breast carcinoma cells in culture. Antibodies against thrombin receptor inhibit thrombin receptor activation and thrombin-induced platelet activation. Furthermore, peptides that resemble the receptor's tethered ligand domain inhibit platelet aggregation by thrombin. P703P may play a role in prostate cancer through a protease-activated receptor on the cancer cell or on stromal cells. The potential trypsin-like protease activity of P703P may either activate a protease-activated receptor on the cancer cell 15 membrane to promote tumorigenesis or activate a protease-activated receptor on the adjacent cells (such as stromal cells) to secrete growth factors and/or proteases (such as matrix metalloproteinases) that could promote tumor angiogenesis, invasion and metastasis. P703P may thus promote tumor progression and/or metastasis through the activation of protease-activated receptor. Polypeptides and antibodies that block the 20 P703P-receptor interaction may therefore be usefully employed in the treatment of prostate cancer.

Further studies using a PCR-based subtraction library of a prostate tumor pool subtracted against a pool of normal tissues (referred to as JP: PCR subtraction) resulted in the isolation of thirteen additional clones, seven of which did not share any 25 significant homology to known GenBank sequences. The determined cDNA sequences for these seven clones (P711P, P712P, novel 23, P774P, P775P, P710P and P768P) are provided in SEQ ID NO: 307-311, 313 and 315, respectively. The remaining six clones (SEQ ID NO: 316 and 321-325) were shown to share some homology to known genes. By microarray analysis, all thirteen clones showed three or more fold over-expression in

prostate tissues, including prostate tumors, BPH and normal prostate as compared to normal non-prostate tissues. Clones P711P, P712P, novel 23 and P768P showed over-expression in most prostate tumors and BPH tissues tested (n=29), and in the majority of normal prostate tissues (n=4), but background to low expression levels in all normal tissues. Clones P774P, P775P and P710P showed comparatively lower expression and expression in fewer prostate tumors and BPH samples, with negative to low expression in normal prostate.

Further studies led to the isolation of an extended cDNA sequence for P712P (SEQ ID NO: 552). The amino acid sequences encoded by 16 predicted open reading frames present within the sequence of SEQ ID NO: 552 are provided in SEQ ID NO: 553-568.

The full-length cDNA for P711P was obtained by employing the partial sequence of SEQ ID NO: 307 to screen a prostate cDNA library. Specifically, a directionally cloned prostate cDNA library was prepared using standard techniques. One million colonies of this library were plated onto LB/Amp plates. Nylon membrane filters were used to lift these colonies, and the cDNAs which were picked up by these filters were denatured and cross-linked to the filters by UV light. The P711P cDNA fragment of SEQ ID NO: 307 was radio-labeled and used to hybridize with these filters. Positive clones were selected, and cDNAs were prepared and sequenced using an automatic Perkin Elmer/Applied Biosystems sequencer. The determined full-length sequence of P711P is provided in SEQ ID NO: 382, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 383.

Using PCR and hybridization-based methodologies, additional cDNA sequence information was derived for two clones described above, 11-C9 and 9-F3, herein after referred to as P707P and P714P, respectively (SEQ ID NO: 333 and 334). After comparison with the most recent GenBank, P707P was found to be a splice variant of the known gene HoxB13. In contrast, no significant homologies to P714P were found. Further studies employing the sequence of SEQ ID NO: 334 as a probe in standard full-length cloning methods, resulted in an extended cDNA sequence for P714P. This sequence

is provided in SEQ ID NO: 698. This sequence was found to show some homology to the gene that encodes human ribosomal L23A protein.

Clones 8-B3, P89, P98, P130 and P201 (as disclosed in U.S. Patent Application No. 09/020,956, filed February 9, 1998) were found to be contained within one contiguous sequence, referred to as P705P (SEQ ID NO: 335, with the predicted amino acid sequence provided in SEQ ID NO: 336), which was determined to be a splice variant of the known gene NKX 3.1.

Further studies on P775P resulted in the isolation of four additional sequences (SEQ ID NO: 473-476) which are all splice variants of the P775P gene. The sequence of SEQ ID NO: 474 was found to contain two open reading frames (ORFs). The predicted amino acid sequences encoded by these ORFs are provided in SEQ ID NO: 477 and 478. The cDNA sequence of SEQ ID NO: 475 was found to contain an ORF which encodes the amino acid sequence of SEQ ID NO: 479. The cDNA sequence of SEQ ID NO: 473 was found to contain four ORFs. The predicted amino acid sequences encoded by these ORFs are provided in SEQ ID NO: 480-483. Additional splice variants of P775P are provided in SEQ ID NO: 593-597.

Subsequent studies led to the identification of a genomic region on chromosome 22q11.2, known as the Cat Eye Syndrome region, that contains the five prostate genes P704P, P712P, P774P, P775P and B305D. The relative location of each of these five genes within the genomic region is shown in Fig. 10. This region may therefore be associated with malignant tumors, and other potential tumor genes may be contained within this region. These studies also led to the identification of a potential open reading frame (ORF) for P775P (provided in SEQ ID NO: 533), which encodes the amino acid sequence of SEQ ID NO: 534.

Comparison of the clone of SEQ ID NO: 325 (referred to as P558S) with sequences in the GenBank and GeneSeq DNA databases showed that P558S is identical to the prostate-specific transglutaminase gene, which is known to have two forms. The full-length sequences for the two forms are provided in SEQ ID NO: 773 and 774, with the corresponding amino acid sequences being provided in SEQ ID NO: 775 and 776,

respectively. The cDNA sequence of SEQ ID NO: 774 has a 15 pair base insert, resulting in a 5 amino acid insert in the corresponding amino acid sequence (SEQ ID NO: 776). This insert is not present in the sequence of SEQ ID NO: 773.

5

EXAMPLE 4

SYNTHESIS OF POLYPEPTIDES

Polypeptides may be synthesized on a Perkin Elmer/Applied Biosystems 430A peptide synthesizer using FMOC chemistry with HPTU (O-Benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate) activation. A Gly-Cys-Gly sequence may be attached to the amino terminus of the peptide to provide a method of conjugation, binding to an immobilized surface, or labeling of the peptide. Cleavage of the peptides from the solid support may be carried out using the following cleavage mixture: trifluoroacetic acid:ethanedithiol:thioanisole:water:phenol (40:1:2:2:3). After cleaving for 2 hours, the peptides may be precipitated in cold methyl-t-butyl-ether. The peptide pellets may then be dissolved in water containing 0.1% trifluoroacetic acid (TFA) and lyophilized prior to purification by C18 reverse phase HPLC. A gradient of 0%-60% acetonitrile (containing 0.1% TFA) in water (containing 0.1% TFA) may be used to elute the peptides. Following lyophilization of the pure fractions, the peptides may be characterized using electrospray or other types of mass spectrometry and by amino acid analysis.

EXAMPLE 5

FURTHER ISOLATION AND CHARACTERIZATION OF PROSTATE-SPECIFIC POLYPEPTIDES BY PCR-BASED SUBTRACTION

25

A cDNA library generated from prostate primary tumor mRNA as described above was subtracted with cDNA from normal prostate. The subtraction was performed using a PCR-based protocol (Clontech), which was modified to generate larger fragments. Within this protocol, tester and driver double stranded cDNA were separately digested with

five restriction enzymes that recognize six-nucleotide restriction sites (MluI, MscI, PvuII, Sall and StuI). This digestion resulted in an average cDNA size of 600 bp, rather than the average size of 300 bp that results from digestion with RsaI according to the Clontech protocol. 5 populations were then created with different adapters, and the driver library remained without adapters.

The tester and driver libraries were then hybridized using excess driver cDNA. In the first hybridization step, driver was separately hybridized with each of the two tester cDNA populations. This resulted in populations of (a) unhybridized tester 10 cDNAs, (b) tester cDNAs hybridized to other tester cDNAs, (c) tester cDNAs hybridized to driver cDNAs and (d) unhybridized driver cDNAs. The two separate hybridization reactions were then combined, and rehybridized in the presence of additional denatured driver cDNA. Following this second hybridization, in addition to populations (a) through 15 (d), a fifth population (e) was generated in which tester cDNA with one adapter hybridized to tester cDNA with the second adapter. Accordingly, the second hybridization step resulted in enrichment of differentially expressed sequences which could be used as templates for PCR amplification with adaptor-specific primers.

The ends were then filled in, and PCR amplification was performed using adaptor-specific primers. Only population (e), which contained tester cDNA that did not 20 hybridize to driver cDNA, was amplified exponentially. A second PCR amplification step was then performed, to reduce background and further enrich differentially expressed sequences.

This PCR-based subtraction technique normalizes differentially expressed cDNAs so that rare transcripts that are overexpressed in prostate tumor tissue may be 25 recoverable. Such transcripts would be difficult to recover by traditional subtraction methods.

In addition to genes known to be overexpressed in prostate tumor, seventy-seven further clones were identified. Sequences of these partial cDNAs are provided in SEQ ID NO: 29 to 305. Most of these clones had no significant homology to database

sequences. Exceptions were JPTPN23 (SEQ ID NO: 231; similarity to pig valosin-containing protein), JPTPN30 (SEQ ID NO: 234; similarity to rat mRNA for proteasome subunit), JPTPN45 (SEQ ID NO: 243; similarity to rat *norvegicus* cytosolic NADP-dependent isocitrate dehydrogenase), JPTPN46 (SEQ ID NO: 244; similarity to human subclone H8 4 d4 DNA sequence), JP1D6 (SEQ ID NO: 265; similarity to *G. gallus* dynein light chain-A), JP8D6 (SEQ ID NO: 288; similarity to human BAC clone RG016J04), JP8F5 (SEQ ID NO: 289; similarity to human subclone H8 3 b5 DNA sequence), and JP8E9 (SEQ ID NO: 299; similarity to human Alu sequence).

Additional studies using the PCR-based subtraction library consisting of a prostate tumor pool subtracted against a normal prostate pool (referred to as PT-PN PCR subtraction) yielded three additional clones. Comparison of the cDNA sequences of these clones with the most recent release of GenBank revealed no significant homologies to the two clones referred to as P715P and P767P (SEQ ID NO: 312 and 314). The remaining clone was found to show some homology to the known gene KIAA0056 (SEQ ID NO: 318). Using microarray analysis to measure mRNA expression levels in various tissues, all three clones were found to be over-expressed in prostate tumors and BPH tissues. Specifically, clone P715P was over-expressed in most prostate tumors and BPH tissues by a factor of three or greater, with elevated expression seen in the majority of normal prostate samples and in fetal tissue, but negative to low expression in all other normal tissues. Clone P767P was over-expressed in several prostate tumors and BPH tissues, with moderate expression levels in half of the normal prostate samples, and background to low expression in all other normal tissues tested.

Further analysis, by microarray as described above, of the PT-PN PCR subtraction library and of a DNA subtraction library containing cDNA from prostate tumor subtracted with a pool of normal tissue cDNAs, led to the isolation of 27 additional clones (SEQ ID NO: 340-365 and 381) which were determined to be over-expressed in prostate tumor. The clones of SEQ ID NO: 341, 342, 345, 347, 348, 349, 351, 355-359, 361, 362 and 364 were also found to be expressed in normal prostate. Expression of all 26 clones in a variety of normal tissues was found to be low or undetectable, with the exception of

P544S (SEQ ID NO: 356) which was found to be expressed in small intestine. Of the 26 clones, 11 (SEQ ID NO: 340-349 and 362) were found to show some homology to previously identified sequences. No significant homologies were found to the clones of SEQ ID NO: 350, 351, 353-361, and 363-365.

5 Comparison of the sequence of SEQ ID NO: 362 with sequences in the GenBank and GeneSeq DNA databases showed that this clone (referred to as P788P) is identical to GeneSeq Accession No. X27262, which encodes a protein found in the GeneSeq protein Accession No. Y00931. The full length cDNA sequence of P788P is shown in Figure 12A (SEQ ID NO: 777), with the corresponding predicted amino acid
10 being shown in Figure 12B (SEQ ID NO: 778). Subsequently, a full-length cDNA sequence for P788P that contains polymorphisms not found in the sequence of SEQ ID NO: 779, was cloned multiple times by PCR amplification from cDNA prepared from several RNA templates from three individuals. This determined cDNA sequence of this polymorphic variant of P788P is provided in SEQ ID NO: 779, with the corresponding
15 amino acid sequence being provided in SEQ ID NO: 780. The sequence of SEQ ID NO: 780 differs from that of SEQ ID NO: 778 by six amino acid residues.

Further studies on the clone of SEQ ID NO: 352 (referred to as P790P) led to the isolation of the full-length cDNA sequence of SEQ ID NO: 526. The corresponding predicted amino acid is provided in SEQ ID NO: 527. Data from two quantitative PCR
20 experiments indicated that P790P is over-expressed in 11/15 tested prostate tumor samples and is expressed at low levels in spinal cord, with no expression being seen in all other normal samples tested. Data from further PCR experiments and microarray experiments showed over-expression in normal prostate and prostate tumor with little or no expression in other tissues tested. P790P was subsequently found to show significant homology to a
25 previously identified G-protein coupled prostate tissue receptor.

Additional studies on the clone of SEQ ID NO: 354 (referred to as P776P) led to the isolation of an extended cDNA sequence, provided in SEQ ID NO: 569. The determined cDNA sequences of three additional splice variants of P776P are provided in SEQ ID NO: 570-572. The amino acid sequences encoded by two predicted open reading

frames (ORFs) contained within SEQ ID NO: 570, one predicted ORF contained within SEQ ID NO: 571, and 11 predicted ORFs contained within SEQ ID NO: 569, are provided in SEQ ID NO: 573-586, respectively.

Comparison of the cDNA sequences for the clones P767P (SEQ ID NO: 514) and P777P (SEQ ID NO: 350) with sequences in the GenBank human EST database showed that the two clones matched many EST sequences in common, suggesting that P767P and P777P may represent the same gene. A DNA consensus sequence derived from a DNA sequence alignment of P767P, P777P and multiple EST clones is provided in SEQ ID NO: 587. The amino acid sequences encoded by three putative ORFs located 10 within SEQ ID NO: 587 are provided in SEQ ID NO: 588-590.

EXAMPLE 6

PEPTIDE PRIMING OF MICE AND PROPAGATION OF CTL LINES

15 6.1. This Example illustrates the preparation of a CTL cell line specific for cells expressing the P502S gene.

Mice expressing the transgene for human HLA A2Kb (provided by Dr L. Sherman, The Scripps Research Institute, La Jolla, CA) were immunized with P2S#12 peptide (VLGWVAEL; SEQ ID NO: 306), which is derived from the P502S gene (also referred to herein as J1-17, SEQ ID NO: 8), as described by Theobald et al., *Proc. Natl. Acad. Sci. USA* 92:11993-11997, 1995 with the following modifications. Mice were immunized with 100 μ g of P2S#12 and 120 μ g of an I-A^b binding peptide derived from hepatitis B Virus protein emulsified in incomplete Freund's adjuvant. Three weeks later these mice were sacrificed and using a nylon mesh single cell suspensions prepared. Cells 25 were then resuspended at 6 x 10⁶ cells/ml in complete media (RPMI-1640; Gibco BRL, Gaithersburg, MD) containing 10% FCS, 2mM Glutamine (Gibco BRL), sodium pyruvate (Gibco BRL), non-essential amino acids (Gibco BRL), 2 x 10⁻⁵ M 2-mercaptoethanol, 50U/ml penicillin and streptomycin, and cultured in the presence of irradiated (3000 rads) P2S#12-pulsed (5mg/ml P2S#12 and 10mg/ml β 2-microglobulin) LPS blasts (A2

transgenic spleens cells cultured in the presence of 7 μ g/ml dextran sulfate and 25 μ g/ml LPS for 3 days). Six days later, cells (5×10^5 /ml) were restimulated with 2.5×10^6 /ml peptide pulsed irradiated (20,000 rads) EL4A2Kb cells (Sherman et al, *Science* 258:815-818, 1992) and 3×10^6 /ml A2 transgenic spleen feeder cells. Cells were cultured in the presence of 20U/ml IL-2. Cells continued to be restimulated on a weekly basis as described, in preparation for cloning the line.

P2S#12 line was cloned by limiting dilution analysis with peptide pulsed EL4 A2Kb tumor cells (1×10^4 cells/ well) as stimulators and A2 transgenic spleen cells as feeders (5×10^5 cells/ well) grown in the presence of 30U/ml IL-2. On day 14, cells were restimulated as before. On day 21, clones that were growing were isolated and maintained in culture. Several of these clones demonstrated significantly higher reactivity (lysis) against human fibroblasts (HLA A2Kb expressing) transduced with P502S than against control fibroblasts. An example is presented in Figure 1.

This data indicates that P2S #12 represents a naturally processed epitope of the P502S protein that is expressed in the context of the human HLA A2Kb molecule.

6.2. This Example illustrates the preparation of murine CTL lines and CTL clones specific for cells expressing the P501S gene.

This series of experiments were performed similarly to that described above. Mice were immunized with the P1S#10 peptide (SEQ ID NO: 337), which is derived from the P501S gene (also referred to herein as L1-12, SEQ ID NO: 110). The P1S#10 peptide was derived by analysis of the predicted polypeptide sequence for P501S for potential HLA-A2 binding sequences as defined by published HLA-A2 binding motifs (Parker, KC, et al, *J. Immunol.*, 152:163, 1994). P1S#10 peptide was synthesized as described in Example 4, and empirically tested for HLA-A2 binding using a T cell based competition assay. Predicted A2 binding peptides were tested for their ability to compete HLA-A2 specific peptide presentation to an HLA-A2 restricted CTL clone (D150M58), which is specific for the HLA-A2 binding influenza matrix peptide fluM58. D150M58 CTL secretes TNF in response to self-presentation of peptide fluM58. In the competition assay,

test peptides at 100-200 µg/ml were added to cultures of D150M58 CTL in order to bind HLA-A2 on the CTL. After thirty minutes, CTL cultured with test peptides, or control peptides, were tested for their antigen dose response to the fluM58 peptide in a standard TNF bioassay. As shown in Figure 3, peptide P1S#10 competes HLA-A2 restricted presentation of fluM58, demonstrating that peptide P1S#10 binds HLA-A2.

Mice expressing the transgene for human HLA A2Kb were immunized as described by Theobald et al. (*Proc. Natl. Acad. Sci. USA* 92:11993-11997, 1995) with the following modifications. Mice were immunized with 62.5µg of P1S #10 and 120µg of an I-A^b binding peptide derived from Hepatitis B Virus protein emulsified in incomplete Freund's adjuvant. Three weeks later these mice were sacrificed and single cell suspensions prepared using a nylon mesh. Cells were then resuspended at 6×10^6 cells/ml in complete media (as described above) and cultured in the presence of irradiated (3000 rads) P1S#10-pulsed (2µg/ml P1S#10 and 10mg/ml β2-microglobulin) LPS blasts (A2 transgenic spleens cells cultured in the presence of 7µg/ml dextran sulfate and 25µg/ml LPS for 3 days). Six days later cells (5×10^5 /ml) were restimulated with 2.5×10^6 /ml peptide-pulsed irradiated (20,000 rads) EL4A2Kb cells, as described above, and 3×10^6 /ml A2 transgenic spleen feeder cells. Cells were cultured in the presence of 20 U/ml IL-2. Cells were restimulated on a weekly basis in preparation for cloning. After three rounds of *in vitro* stimulations, one line was generated that recognized P1S#10-pulsed Jurkat A2Kb targets and P501S-transduced Jurkat targets as shown in Figure 4.

A P1S#10-specific CTL line was cloned by limiting dilution analysis with peptide pulsed EL4 A2Kb tumor cells (1×10^4 cells/ well) as stimulators and A2 transgenic spleen cells as feeders (5×10^5 cells/ well) grown in the presence of 30U/ml IL-2. On day 14, cells were restimulated as before. On day 21, viable clones were isolated and maintained in culture. As shown in Figure 5, five of these clones demonstrated specific cytolytic reactivity against P501S-transduced Jurkat A2Kb targets. This data indicates that P1S#10 represents a naturally processed epitope of the P501S protein that is expressed in the context of the human HLA-A2.1 molecule.

EXAMPLE 7

PRIMING OF CTL *IN VIVO* USING NAKED DNA IMMUNIZATION
WITH A PROSTATE ANTIGEN

The prostate-specific antigen L1-12, as described above, is also referred to
5 as P501S. HLA A2Kb Tg mice (provided by Dr L. Sherman, The Scripps Research
Institute, La Jolla, CA) were immunized with 100 µg P501S in the vector VR1012 either
intramuscularly or intradermally. The mice were immunized three times, with a two week
interval between immunizations. Two weeks after the last immunization, immune spleen
cells were cultured with Jurkat A2Kb-P501S transduced stimulator cells. CTL lines were
10 stimulated weekly. After two weeks of *in vitro* stimulation, CTL activity was assessed
against P501S transduced targets. Two out of 8 mice developed strong anti-P501S CTL
responses. These results demonstrate that P501S contains at least one naturally processed
HLA-A2-restricted CTL epitope.

15

EXAMPLE 8

ABILITY OF HUMAN T CELLS TO RECOGNIZE PROSTATE-SPECIFIC POLYPEPTIDES

This Example illustrates the ability of T cells specific for a prostate tumor
polypeptide to recognize human tumor.

20 Human CD8⁺ T cells were primed *in vitro* to the P2S-12 peptide (SEQ ID
NO: 306) derived from P502S (also referred to as J1-17) using dendritic cells according to
the protocol of Van Tsai et al. (*Critical Reviews in Immunology* 18:65-75, 1998). The
resulting CD8⁺ T cell microcultures were tested for their ability to recognize the P2S-12
peptide presented by autologous fibroblasts or fibroblasts which were transduced to express
25 the P502S gene in a γ-interferon ELISPOT assay (see Lalvani et al., *J. Exp. Med.* 186:859-
865, 1997). Briefly, titrating numbers of T cells were assayed in duplicate on 10⁴
fibroblasts in the presence of 3 µg/ml human β₂-microglobulin and 1 µg/ml P2S-12 peptide
or control E75 peptide. In addition, T cells were simultaneously assayed on autologous
fibroblasts transduced with the P502S gene or as a control, fibroblasts transduced with

HER-2/*neu*. Prior to the assay, the fibroblasts were treated with 10 ng/ml γ -interferon for 48 hours to upregulate class I MHC expression. One of the microcultures (#5) demonstrated strong recognition of both peptide pulsed fibroblasts as well as transduced fibroblasts in a γ -interferon ELISPOT assay. Figure 2A demonstrates that there was a 5 strong increase in the number of γ -interferon spots with increasing numbers of T cells on fibroblasts pulsed with the P2S-12 peptide (solid bars) but not with the control E75 peptide (open bars). This shows the ability of these T cells to specifically recognize the P2S-12 peptide. As shown in Figure 2B, this microculture also demonstrated an increase in the 10 number of γ -interferon spots with increasing numbers of T cells on fibroblasts transduced to express the P502S gene but not the HER-2/*neu* gene. These results provide additional confirmatory evidence that the P2S-12 peptide is a naturally processed epitope of the P502S protein. Furthermore, this also demonstrates that there exists in the human T cell repertoire, high affinity T cells which are capable of recognizing this epitope. These T cells should also be capable of recognizing human tumors which express the P502S gene.

15

EXAMPLE 9

ELICITATION OF PROSTATE ANTIGEN-SPECIFIC CTL RESPONSES IN HUMAN BLOOD

20 This Example illustrates the ability of a prostate-specific antigen to elicit a CTL response in blood of normal humans.

Autologous dendritic cells (DC) were differentiated from monocyte cultures derived from PBMC of normal donors by growth for five days in RPMI medium containing 10% human serum, 50 ng/ml GMCSF and 30 ng/ml IL-4. Following culture, DC were 25 infected overnight with recombinant P501S-expressing vaccinia virus at an M.O.I. of 5 and matured for 8 hours by the addition of 2 micrograms/ml CD40 ligand. Virus was inactivated by UV irradiation, CD8⁺ cells were isolated by positive selection using magnetic beads, and priming cultures were initiated in 24-well plates. Following five stimulation cycles using autologous fibroblasts retrovirally transduced to express P501S

and CD80, CD8+ lines were identified that specifically produced interferon-gamma when stimulated with autologous P501S-transduced fibroblasts. The P501S-specific activity of cell line 3A-1 could be maintained following additional stimulation cycles on autologous B-LCL transduced with P501S. Line 3A-1 was shown to specifically recognize autologous 5 B-LCL transduced to express P501S, but not EGFP-transduced autologous B-LCL, as measured by cytotoxicity assays (^{51}Cr release) and interferon-gamma production (Interferon-gamma Elispot; *see above* and Lalvani et al., *J. Exp. Med.* 186:859-865, 1997). The results of these assays are presented in Figures 6A and 6B.

10

EXAMPLE 10

IDENTIFICATION OF A NATURALLY PROCESSED CTL EPITOPE CONTAINED WITHIN A PROSTATE-SPECIFIC ANTIGEN

The 9-mer peptide p5 (SEQ ID NO: 338) was derived from the P703P 15 antigen (also referred to as P20). The p5 peptide is immunogenic in human HLA-A2 donors and is a naturally processed epitope. Antigen specific human CD8+ T cells can be primed following repeated *in vitro* stimulations with monocytes pulsed with p5 peptide. These CTL specifically recognize p5-pulsed and P703P-transduced target cells in both ELISPOT (as described above) and chromium release assays. Additionally, immunization 20 of HLA-A2Kb transgenic mice with p5 leads to the generation of CTL lines which recognize a variety of HLA-A2Kb or HLA-A2 transduced target cells expressing P703P.

Initial studies demonstrating that p5 is a naturally processed epitope were done using HLA-A2Kb transgenic mice. HLA-A2Kb transgenic mice were immunized subcutaneously in the footpad with 100 μg of p5 peptide together with 140 μg of hepatitis 25 B virus core peptide (a Th peptide) in Freund's incomplete adjuvant. Three weeks post immunization, spleen cells from immunized mice were stimulated *in vitro* with peptide-pulsed LPS blasts. CTL activity was assessed by chromium release assay five days after primary *in vitro* stimulation. Retrovirally transduced cells expressing the control antigen

P703P and HLA-A2K_b were used as targets. CTL lines that specifically recognized both p5-pulsed targets as well as P703P-expressing targets were identified.

Human *in vitro* priming experiments demonstrated that the p5 peptide is immunogenic in humans. Dendritic cells (DC) were differentiated from monocyte cultures 5 derived from PBMC of normal human donors by culturing for five days in RPMI medium containing 10% human serum, 50 ng/ml human GM-CSF and 30 ng/ml human IL-4. Following culture, the DC were pulsed with 1 ug/ml p5 peptide and cultured with CD8+ T cell enriched PBMC. CTL lines were restimulated on a weekly basis with p5-pulsed 10 monocytes. Five to six weeks after initiation of the CTL cultures, CTL recognition of p5-pulsed target cells was demonstrated. CTL were additionally shown to recognize human cells transduced to express P703P, demonstrating that p5 is a naturally processed epitope.

Studies identifying a further peptide epitope (referred to as peptide 4) derived from the prostate tumor-specific antigen P703P that is capable of being recognized by CD4 T cells on the surface of cells in the context of HLA class II molecules were 15 carried out as follows. The amino acid sequence for peptide 4 is provided in SEQ ID NO: 781, with the corresponding cDNA sequence being provided in SEQ ID NO: 782.

Twenty 15-mer peptides overlapping by 10 amino acids and derived from the carboxy-terminal fragment of P703P were generated using standard procedures. Dendritic cells (DC) were derived from PBMC of a normal female donor using GM-CSF 20 and IL-4 by standard protocols. CD4 T cells were generated from the same donor as the DC using MACS beads and negative selection. DC were pulsed overnight with pools of the 15-mer peptides, with each peptide at a final concentration of 0.25 microgram/ml. Pulsed DC were washed and plated at 1 x 10⁴ cells/well of 96-well V-bottom plates and purified CD4 T cells were added at 1 x 10⁵/well. Cultures were supplemented with 60 ng/ml IL-6 and 10 ng/ml IL-12 and incubated at 37 °C. Cultures were restimulated as 25 above on a weekly basis using DC generated and pulsed as above as antigen presenting cells, supplemented with 5 ng/ml IL-7 and 10 u/ml IL-2. Following 4 *in vitro* stimulation cycles, 96 lines (each line corresponding to one well) were tested for specific proliferation

and cytokine production in response to the stimulating pools with an irrelevant pool of peptides derived from gammaglobin being used as a control.

One line (referred to as 1-F9) was identified from pool #1 that demonstrated specific proliferation (measured by ³H proliferation assays) and cytokine production (measured by interferon-gamma ELISA assays) in response to pool #1 of P703P peptides. This line was further tested for specific recognition of the peptide pool, specific recognition of individual peptides in the pool, and in HLA mismatch analyses to identify the relevant restricting allele. Line 1-F9 was found to specifically proliferate and produce interferon-gamma in response to peptide pool #1, and also to peptide 4 (SEQ ID NO: 781). Peptide 4 corresponds to amino acids 126-140 of SEQ ID NO: 327. Peptide titration experiments were conducted to assess the sensitivity of line 1-F9 for the specific peptide. The line was found to specifically respond to peptide 4 at concentrations as low as 0.25 ng/ml, indicating that the T cells are very sensitive and therefore likely to have high affinity for the epitope.

To determine the HLA restriction of the P703P response, a panel of antigen presenting cells (APC) was generated that was partially matched with the donor used to generate the T cells. The APC were pulsed with the peptide and used in proliferation and cytokine assays together with line 1-F9. APC matched with the donor at HLA-DRB0701 and HLA-DQB02 alleles were able to present the peptide to the T cells, indicating that the P703P-specific response is restricted to one of these alleles.

In further studies, twenty-four 15-mer peptides overlapping by 10 amino acids and derived from the N-terminal fragment of P703P (corresponding to amino acids 27-154 of SEQ ID NO: 525) were generated by standard procedures and their ability to be recognized by CD4 cells was determined essentially as described above. DC were pulsed overnight with pools of the peptides with each peptide at a final concentration of 10 microgram/ml. A large number of individual CD4 T cell lines (65/480) demonstrated significant proliferation and cytokine release (IFN-gamma) in response to the P703P peptide pools but not to a control peptide pool. The CD4 T cell lines which demonstrated specific activity were restimulated on the appropriate pool of P703P peptides and reassayed on the individual peptides of each pool as well as a peptide dose titration of the pool of peptides in a IFN-gamma release assay and in a proliferation assay.

Sixteen immunogenic peptides were recognized by the T cells from the entire set of peptide antigens tested. The amino acid sequences of these peptides are provided in SEQ ID NO: 799-814, with the corresponding cDNA sequences being provided in SEQ ID NO: 783-798, respectively. In some cases the peptide reactivity of the
5 T cell line could be mapped to a single peptide, however some could be mapped to more than one peptide in each pool. Those CD4 T cell lines that displayed a representative pattern of recognition from each peptide pool with a reasonable affinity for peptide were chosen for further analysis (I-1A, -6A; II-4C, -5E; III-6E, IV-4B, -3F, -9B, -10F, V-5B, -
4D, and -10F). These CD4 T cells lines were restimulated on the appropriate individual
10 peptide and reassayed on autologous DC pulsed with a truncated form of recombinant P703P protein made in *E. coli* (a.a. 96 - 254 of SEQ ID NO: 525), full-length P703P made in the baculovirus expression system, and a fusion between influenza virus NS1 and P703P made in *E. coli*. Of the T cell lines tested, line I-1A recognized specifically the truncated form of P703P (*E. coli*) but no other recombinant form of P703P. This line also recognized
15 the peptide used to elicit the T cells. Line 2-4C recognized the truncated form of P703P (*E. coli*) and the full length form of P703P made in baculovirus, as well as peptide. The remaining T cell lines tested were either peptide-specific only (II-5E, II-6F, IV-4B, IV-3F, IV-9B, IV-10F, V-5B and V-4D) or were non-responsive to any antigen tested (V-10F). These results demonstrate that the peptide sequence RPLLANDLMLIKLDE (SEQ ID NO:
20 814; corresponding to a.a. 110-124 of SEQ ID NO: 525) recognized by the T cell line I-1A, and the peptide sequences SVSESDTIRSIAS (SEQ ID NO: 811; corresponding to a.a. 125-139 of SEQ ID NO: 525) and ISIASQCPTAGNSCL (SEQ ID NO: 810; corresponding to a.a. 135-149 of SEQ ID NO: 525) recognized by the T cell line II-4C may be naturally processed epitopes of the P703P protein.

25

EXAMPLE 11
EXPRESSION OF A BREAST TUMOR-DERIVED ANTIGEN
IN PROSTATE

5 Isolation of the antigen B305D from breast tumor by differential display is described in US Patent Application No. 08/700,014, filed August 20, 1996. Several different splice forms of this antigen were isolated. The determined cDNA sequences for these splice forms are provided in SEQ ID NO: 366-375, with the predicted amino acid sequences corresponding to the sequences of SEQ ID NO: 292, 298 and 301-303 being
10 provided in SEQ ID NO: 299-306, respectively. In further studies, a splice variant of the cDNA sequence of SEQ ID NO: 366 was isolated which was found to contain an additional guanine residue at position 884 (SEQ ID NO: 530), leading to a frameshift in the open reading frame. The determined DNA sequence of this ORF is provided in SEQ ID NO: 531. This frameshift generates a protein sequence (provided in SEQ ID NO: 532) of 293
15 amino acids that contains the C-terminal domain common to the other isoforms of B305D but that differs in the N-terminal region.

The expression levels of B305D in a variety of tumor and normal tissues were examined by real time PCR and by Northern analysis. The results indicated that B305D is highly expressed in breast tumor, prostate tumor, normal prostate and normal
20 testes, with expression being low or undetectable in all other tissues examined (colon tumor, lung tumor, ovary tumor, and normal bone marrow, colon, kidney, liver, lung, ovary, skin, small intestine, stomach). Using real-time PCR on a panel of prostate tumors, expression of B305D in prostate tumors was shown to increase with increasing Gleason grade, demonstrating that expression of B305D increases as prostate cancer progresses.

EXAMPLE 12

GENERATION OF HUMAN CTL *IN VITRO* USING WHOLE GENE PRIMING AND STIMULATION
TECHNIQUES WITH PROSTATE-SPECIFIC ANTIGEN

Using *in vitro* whole-gene priming with P501S-vaccinia infected DC (see, for example, Yee et al, *The Journal of Immunology*, 157(9):4079-86, 1996), human CTL lines were derived that specifically recognize autologous fibroblasts transduced with P501S (also known as L1-12), as determined by interferon- γ ELISPOT analysis as described above. Using a panel of HLA-mismatched B-LCL lines transduced with P501S, these CTL lines were shown to be likely restricted to HLAB class I allele. Specifically, dendritic cells (DC) were differentiated from monocyte cultures derived from PBMC of normal human donors by growing for five days in RPMI medium containing 10% human serum, 50 ng/ml human GM-CSF and 30 ng/ml human IL-4. Following culture, DC were infected overnight with recombinant P501S vaccinia virus at a multiplicity of infection (M.O.I.) of five, and matured overnight by the addition of 3 μ g/ml CD40 ligand. Virus was inactivated by UV irradiation. CD8+ T cells were isolated using a magnetic bead system, and priming cultures were initiated using standard culture techniques. Cultures were restimulated every 7-10 days using autologous primary fibroblasts retrovirally transduced with P501S and CD80. Following four stimulation cycles, CD8+ T cell lines were identified that specifically produced interferon- γ when stimulated with P501S and CD80-transduced autologous fibroblasts. A panel of HLA-mismatched B-LCL lines transduced with P501S were generated to define the restriction allele of the response. By measuring interferon- γ in an ELISPOT assay, the P501S specific response was shown to be likely restricted by HLA B alleles. These results demonstrate that a CD8+ CTL response to P501S can be elicited.

To identify the epitope(s) recognized, cDNA encoding P501S was fragmented by various restriction digests, and sub-cloned into the retroviral expression vector pBIB-KS. Retroviral supernatants were generated by transfection of the helper packaging line Phoenix-Ampho. Supernatants were then used to transduce Jurkat/A2Kb cells for CTL screening. CTL were screened in IFN-gamma ELISPOT assays against these

A2Kb targets transduced with the “library” of P501S fragments. Initial positive fragments P501S/H3 and P501S/F2 were sequenced and found to encode amino acids 106-553 and amino acids 136-547, respectively, of SEQ ID NO: 113. A truncation of H3 was made to encode amino acid residues 106-351 of SEQ ID NO: 113, which was unable to stimulate
5 the CTL, thus localizing the epitope to amino acid residues 351-547. Additional fragments encoding amino acids 1-472 (Fragment A) and amino acids 1-351 (Fragment B) were also constructed. Fragment A but not Fragment B stimulated the CTL thus localizing the epitope to amino acid residues 351-472. Overlapping 20-mer and 18-mer peptides representing this region were tested by pulsing Jurkat/A2Kb cells versus CTL in an IFN-
10 gamma assay. Only peptides P501S-369(20) and P501S-369(18) stimulated the CTL. Nine-mer and 10-mer peptides representing this region were synthesized and similarly tested. Peptide P501S-370 (SEQ ID NO: 539) was the minimal 9-mer giving a strong response. Peptide P501S-376 (SEQ ID NO: 540) also gave a weak response, suggesting that it might represent a cross-reactive epitope.

15 In subsequent studies, the ability of primary human B cells transduced with P501S to prime MHC class I-restricted, P501S-specific, autologous CD8 T cells was examined. Primary B cells were derived from PBMC of a homozygous HLA-A2 donor by culture in CD40 ligand and IL-4, transduced at high frequency with recombinant P501S in the vector pBIB, and selected with blastocidin-S. For *in vitro* priming, purified CD8+ T
20 cells were cultured with autologous CD40 ligand + IL-4 derived, P501S-transduced B cells in a 96-well microculture format. These CTL microcultures were re-stimulated with P501S-transduced B cells and then assayed for specificity. Following this initial screen, microcultures with significant signal above background were cloned on autologous EBV-transformed B cells (BLCL), also transduced with P501S. Using IFN-gamma ELISPOT
25 for detection, several of these CD8 T cell clones were found to be specific for P501S, as demonstrated by reactivity to BLCL/P501S but not BLCL transduced with control antigen. It was further demonstrated that the anti-P501S CD8 T cell specificity is HLA-A2-restricted. First, antibody blocking experiments with anti-HLA-A,B,C monoclonal antibody (W6.32), anti-HLA-B,C monoclonal antibody (B1.23.2) and a control monoclonal antibody

antibody showed that only the anti-HLA-A,B,C antibody blocked recognition of P501S-expressing autologous BLCL. Secondly, the anti-P501S CTL also recognized an HLA-A2 matched, heterologous BLCL transduced with P501S, but not the corresponding EGFP transduced control BLCL.

5

EXAMPLE 13
IDENTIFICATION OF PROSTATE-SPECIFIC ANTIGENS
BY MICROARRAY ANALYSIS

10 This Example describes the isolation of certain prostate-specific polypeptides from a prostate tumor cDNA library.

A human prostate tumor cDNA expression library as described above was screened using microarray analysis to identify clones that display at least a three fold over-expression in prostate tumor and/or normal prostate tissue, as compared to non-prostate 15 normal tissues (not including testis). 372 clones were identified, and 319 were successfully sequenced. Table I presents a summary of these clones, which are shown in SEQ ID NOs:385-400. Of these sequences SEQ ID NOs:386, 389, 390 and 392 correspond to novel genes, and SEQ ID NOs: 393 and 396 correspond to previously identified sequences. The others (SEQ ID NOs:385, 387, 388, 391, 394, 395 and 397-400) correspond to known 20 sequences, as shown in Table I.

Table I

Summary of Prostate Tumor Antigens

Known Genes	Previously Identified Genes	Novel Genes
T-cell gamma chain	P504S	23379 (SEQ ID NO:389)
Kallikrein	P1000C	23399 (SEQ ID NO:392)
Vector	P501S	23320 (SEQ ID NO:386)
CGI-82 protein mRNA (23319; SEQ ID NO:385)	P503S	23381 (SEQ ID NO:390)
PSA	P510S	
Ald. 6 Dehyd.	P784P	
L-iditol-2 dehydrogenase (23376; SEQ ID NO:388)	P502S	
Ets transcription factor PDEF (22672; SEQ ID NO:398)	P706P	
hTGR (22678; SEQ ID NO:399)	19142.2, bangur.seq (22621; SEQ ID NO:396)	
KIAA0295(22685; SEQ ID NO:400)	5566.1 Wang (23404; SEQ ID NO:393)	
Prostatic Acid Phosphatase(22655; SEQ ID NO:397)	P712P	
transglutaminase (22611; SEQ ID NO:395)	P778P	
HDLBP (23508; SEQ ID NO:394)		
CGI-69 Protein(23367; SEQ ID NO:387)		
KIAA0122(23383; SEQ ID NO:391)		
TEEG		

CGI-82 showed 4.06 fold over-expression in prostate tissues as compared to 5 other normal tissues tested. It was over-expressed in 43% of prostate tumors, 25% normal

prostate, not detected in other normal tissues tested. L-iditol-2 dehydrogenase showed 4.94 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 90% of prostate tumors, 100% of normal prostate, and not detected in other normal tissues tested. Ets transcription factor PDEF showed 5.55 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 47% prostate tumors, 25% normal prostate and not detected in other normal tissues tested. hTGR1 showed 9.11 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 63% of prostate tumors and is not detected in normal tissues tested including normal prostate. KIAA0295 showed 5.59 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 47% of prostate tumors, low to undetectable in normal tissues tested including normal prostate tissues. Prostatic acid phosphatase showed 9.14 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 67% of prostate tumors, 50% of normal prostate, and not detected in other normal tissues tested.

Transglutaminase showed 14.84 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 30% of prostate tumors, 50% of normal prostate, and is not detected in other normal tissues tested. High density lipoprotein binding protein (HDLBP) showed 28.06 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 97% of prostate tumors, 75% of normal prostate, and is undetectable in all other normal tissues tested. CGI-69 showed 3.56 fold over-expression in prostate tissues as compared to other normal tissues tested. It is a low abundant gene, detected in more than 90% of prostate tumors, and in 75% normal prostate tissues. The expression of this gene in normal tissues was very low. KIAA0122 showed 4.24 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 57% of prostate tumors, it was undetectable in all normal tissues tested including normal prostate tissues. 19142.2 bangur showed 23.25 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 97% of prostate tumors and 100% of normal prostate. It was undetectable in other normal tissues tested. 5566.1 Wang showed 3.31 fold over-

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expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 97% of prostate tumors, 75% normal prostate and was also over-expressed in normal bone marrow, pancreas, and activated PBMC. Novel clone 23379 (also referred to as P553S) showed 4.86 fold over-expression in prostate tissues as compared to other 5 normal tissues tested. It was detectable in 97% of prostate tumors and 75% normal prostate and is undetectable in all other normal tissues tested. Novel clone 23399 showed 4.09 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 27% of prostate tumors and was undetectable in all normal tissues tested including normal prostate tissues. Novel clone 23320 showed 3.15 fold over-expression in 10 prostate tissues as compared to other normal tissues tested. It was detectable in all prostate tumors and 50% of normal prostate tissues. It was also expressed in normal colon and trachea. Other normal tissues do not express this gene at high level.

Subsequent full-length cloning studies on P553S, using standard techniques, revealed that this clone is an incomplete spliced form of P501S. The determined cDNA 15 sequences for four splice variants of P553S are provided in SEQ ID NO: 702-705. An amino acid sequence encoded by SEQ ID NO: 705 is provided in SEQ ID NO: 706. The cDNA sequence of SEQ ID NO: 702 was found to contain two open reading frames (ORFs). The amino acid sequences encoded by these two ORFs are provided in SEQ ID NO: 707 and 708.

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EXAMPLE 14
IDENTIFICATION OF PROSTATE-SPECIFIC ANTIGENS
BY ELECTRONIC SUBTRACTION

25 This Example describes the use of an electronic subtraction technique to identify prostate-specific antigens.

Potential prostate-specific genes present in the GenBank human EST database were identified by electronic subtraction (similar to that described by Vasmatzis et al., *Proc. Natl. Acad. Sci. USA* 95:300-304, 1998). The sequences of EST clones

(43,482) derived from various prostate libraries were obtained from the GenBank public human EST database. Each prostate EST sequence was used as a query sequence in a BLASTN (National Center for Biotechnology Information) search against the human EST database. All matches considered identical (length of matching sequence >100 base pairs, 5 density of identical matches over this region > 70%) were grouped (aligned) together in a cluster. Clusters containing more than 200 ESTs were discarded since they probably represented repetitive elements or highly expressed genes such as those for ribosomal proteins. If two or more clusters shared common ESTs, those clusters were grouped together into a “supercluster,” resulting in 4,345 prostate superclusters.

10 Records for the 479 human cDNA libraries represented in the GenBank release were downloaded to create a database of these cDNA library records. These 479 cDNA libraries were grouped into three groups: Plus (normal prostate and prostate tumor libraries, and breast cell line libraries, in which expression was desired), Minus (libraries from other normal adult tissues, in which expression was not desirable), and Other 15 (libraries from fetal tissue, infant tissue, tissues found only in women, non-prostate tumors and cell lines other than prostate cell lines, in which expression was considered to be irrelevant). A summary of these library groups is presented in Table II.

Table II

Prostate cDNA Libraries and ESTs

Library	# of Libraries	# of ESTs
Plus	25	43,482
Normal	11	18,875
Tumor	11	21,769
Cell lines	3	2,838
Minus	166	
Other	287	

Each supercluster was analyzed in terms of the ESTs within the supercluster. The tissue source of each EST clone was noted and used to classify the superclusters into four groups: Type 1- EST clones found in the Plus group libraries only; no expression detected in Minus or Other group libraries; Type 2- EST clones derived from the Plus and Other group libraries only; no expression detected in the Minus group; Type 3- EST clones derived from the Plus, Minus and Other group libraries, but the number of ESTs derived from the Plus group is higher than in either the Minus or Other groups; and Type 4- EST clones derived from Plus, Minus and Other group libraries, but the number derived from the Plus group is higher than the number derived from the Minus group. This analysis identified 4,345 breast clusters (*see* Table III). From these clusters, 3,172 EST clones were ordered from Research Genetics, Inc., and were received as frozen glycerol stocks in 96-well plates.

Table III
Prostate Cluster Summary

Type	# of Superclusters	# of ESTs Ordered
1	688	677
2	2899	2484
3	85	11
4	673	0
Total	4345	3172

The EST clone inserts were PCR-amplified using amino-linked PCR primers for Synteni microarray analysis. When more than one PCR product was obtained for a particular clone, that PCR product was not used for expression analysis. In total, 2,528 clones from the electronic subtraction method were analyzed by microarray analysis to identify electronic subtraction breast clones that had high levels of tumor vs. normal

tissue mRNA. Such screens were performed using a Synteni (Palo Alto, CA) microarray, according to the manufacturer's instructions (and essentially as described by Schena et al., *Proc. Natl. Acad. Sci. USA* 93:10614-10619, 1996 and Heller et al., *Proc. Natl. Acad. Sci. USA* 94:2150-2155, 1997). Within these analyses, the clones were arrayed on the chip, which was then probed with fluorescent probes generated from normal and tumor prostate cDNA, as well as various other normal tissues. The slides were scanned and the fluorescence intensity was measured.

Clones with an expression ratio greater than 3 (*i.e.*, the level in prostate tumor and normal prostate mRNA was at least three times the level in other normal tissue mRNA) were identified as prostate tumor-specific sequences (Table IV). The sequences of these clones are provided in SEQ ID NO: 401-453, with certain novel sequences shown in SEQ ID NO: 407, 413, 416-419, 422, 426, 427 and 450.

Table IV

15 Prostate-tumor Specific Clones

SEQ ID NO.	Sequence Designation	Comments
401	22545	previously identified P1000C
402	22547	previously identified P704P
403	22548	known
404	22550	known
405	22551	PSA
406	22552	prostate secretory protein 94
407	22553	novel
408	22558	previously identified P509S
409	22562	glandular kallikrein
410	22565	previously identified P1000C
411	22567	PAP
412	22568	B1006C (breast tumor antigen)
413	22570	novel
414	22571	PSA
415	22572	previously identified P706P
416	22573	novel
417	22574	novel

418	22575	novel
419	22580	novel
420	22581	PAP
421	22582	prostatic secretory protein 94
422	22583	novel
423	22584	prostatic secretory protein 94
424	22585	prostatic secretory protein 94
425	22586	known
426	22587	novel
427	22588	novel
428	22589	PAP
429	22590	known
430	22591	PSA
431	22592	known
432	22593	Previously identified P777P
433	22594	T cell receptor gamma chain
434	22595	Previously identified P705P
435	22596	Previously identified P707P
436	22847	PAP
437	22848	known
438	22849	prostatic secretory protein 57
439	22851	PAP
440	22852	PAP
441	22853	PAP
442	22854	previously identified P509S
443	22855	previously identified P705P
444	22856	previously identified P774P
445	22857	PSA
446	23601	previously identified P777P
447	23602	PSA
448	23605	PSA
449	23606	PSA
450	23612	novel
451	23614	PSA
452	23618	previously identified P1000C
453	23622	previously identified P705P

Further studies on the clone of SEQ ID NO: 407 (also referred to as P1020C) led to the isolation of an extended cDNA sequence provided in SEQ ID NO: 591. This extended cDNA sequence was found to contain an open reading frame that encodes

the predicted amino acid sequence of SEQ ID NO: 592. The P1020C cDNA and amino acid sequences were found to show some similarity to the human endogenous retroviral HERV-K pol gene and protein.

5

EXAMPLE 15

FURTHER IDENTIFICATION OF PROSTATE-SPECIFIC ANTIGENS BY MICROARRAY ANALYSIS

This Example describes the isolation of additional prostate-specific polypeptides from a prostate tumor cDNA library.

10

A human prostate tumor cDNA expression library as described above was screened using microarray analysis to identify clones that display at least a three fold over-expression in prostate tumor and/or normal prostate tissue, as compared to non-prostate normal tissues (not including testis). 142 clones were identified and sequenced. Certain of these clones are shown in SEQ ID NO: 454-467. Of these sequences, SEQ ID NO: 459-15 461 represent novel genes. The others (SEQ ID NO: 454-458 and 461-467) correspond to known sequences.

EXAMPLE 16

FURTHER CHARACTERIZATION OF PROSTATE-SPECIFIC ANTIGEN P710P

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This Example describes the full length cloning of P710P.

The prostate cDNA library described above was screened with the P710P fragment described above. One million colonies were plated on LB/Ampicillin plates. Nylon membrane filters were used to lift these colonies, and the cDNAs picked up by these 25 filters were then denatured and cross-linked to the filters by UV light. The P710P fragment was radiolabeled and used to hybridize with the filters. Positive cDNA clones were selected and their cDNAs recovered and sequenced by an automatic Perkin Elmer/Applied Biosystems Division Sequencer. Four sequences were obtained, and are presented in SEQ ID NO: 468-471. These sequences appear to represent different splice variants of the

P710P gene. Subsequent comparison of the cDNA sequences of P710P with those in Genbank revealed homology to the DD3 gene (Genbank accession numbers AF103907 & AF103908). The cDNA sequence of DD3 is provided in SEQ ID NO: 690.

5

EXAMPLE 17

PROTEIN EXPRESSION OF THE PROSTATE-SPECIFIC ANTIGEN P501S

This example describes the expression and purification of the prostate-specific antigen P501S in *E. coli*, baculovirus and mammalian cells.

10 A) **EXPRESSION IN *E. COLI***

Expression of the full-length form of P501S was attempted by first cloning P501S without the leader sequence (amino acids 36-553 of SEQ ID NO: 113) downstream of the first 30 amino acids of the *M. tuberculosis* antigen Ra12 (SEQ ID NO: 484) in pET17b. Specifically, P501S DNA was used to perform PCR using the primers AW025 (SEQ ID NO: 485) and AW003 (SEQ ID NO: 486). AW025 is a sense cloning primer that contains a HindIII site. AW003 is an antisense cloning primer that contains an EcoRI site. DNA amplification was performed using 5 µl 10X Pfu buffer, 1 µl 20 mM dNTPs, 1 µl each of the PCR primers at 10 µM concentration, 40 µl water, 1 µl Pfu DNA polymerase (Stratagene, La Jolla, CA) and 1 µl DNA at 100 ng/µl. Denaturation at 95°C was performed for 30 sec, followed by 10 cycles of 95°C for 30 sec, 60°C for 1 min and by 72°C for 3 min. 20 cycles of 95°C for 30 sec, 65°C for 1 min and by 72°C for 3 min, and lastly by 1 cycle of 72°C for 10 min. The PCR product was cloned to Ra12m/pET17b using HindIII and EcoRI. The sequence of the resulting fusion construct (referred to as Ra12-P501S-F) was confirmed by DNA sequencing.

25 The fusion construct was transformed into BL21(DE3)pLysE, pLysS and CodonPlus *E. coli* (Stratagene) and grown overnight in LB broth with kanamycin. The resulting culture was induced with IPTG. Protein was transferred to PVDF membrane and blocked with 5% non-fat milk (in PBS-Tween buffer), washed three times and incubated

with mouse anti-His tag antibody (Clontech) for 1 hour. The membrane was washed 3 times and probed with HRP-Protein A (Zymed) for 30 min. Finally, the membrane was washed 3 times and developed with ECL (Amersham). No expression was detected by Western blot. Similarly, no expression was detected by Western blot when the Ra12-
5 P501S-F fusion was used for expression in BL21CodonPlus by CE6 phage (Invitrogen).

An N-terminal fragment of P501S (amino acids 36-325 of SEQ ID NO: 113) was cloned down-stream of the first 30 amino acids of the *M. tuberculosis* antigen Ra12 in pET17b as follows. P501S DNA was used to perform PCR using the primers AW025 (SEQ ID NO: 485) and AW027 (SEQ ID NO: 487). AW027 is an antisense cloning primer that
10 contains an EcoRI site and a stop codon. DNA amplification was performed essentially as described above. The resulting PCR product was cloned to Ra12 in pET17b at the HindIII and EcoRI sites. The fusion construct (referred to as Ra12-P501S-N) was confirmed by DNA sequencing.

The Ra12-P501S-N fusion construct was used for expression in
15 BL21(DE3)pLysE, pLysS and CodonPlus, essentially as described above. Using Western blot analysis, protein bands were observed at the expected molecular weight of 36 kDa. Some high molecular weight bands were also observed, probably due to aggregation of the recombinant protein. No expression was detected by Western blot when the Ra12-P501S-F fusion was used for expression in BL21CodonPlus by CE6 phage.

A fusion construct comprising a C-terminal portion of P501S (amino acids
20 257-553 of SEQ ID NO: 113) located down-stream of the first 30 amino acids of the *M. tuberculosis* antigen Ra12 (SEQ ID NO: 484) was prepared as follows. P501S DNA was used to perform PCR using the primers AW026 (SEQ ID NO: 488) and AW003 (SEQ ID NO: 486). AW026 is a sense cloning primer that contains a HindIII site. DNA
25 amplification was performed essentially as described above. The resulting PCR product was cloned to Ra12 in pET17b at the HindIII and EcoRI sites. The sequence for the fusion construct (referred to as Ra12-P501S-C) was confirmed.

The Ra12-P501S-C fusion construct was used for expression in BL21(DE3)pLysE, pLysS and CodonPlus, as described above. A small amount of protein

210121.427C15

was detected by Western blot, with some molecular weight aggregates also being observed. Expression was also detected by Western blot when the Ra12-P501S-C fusion was used for expression in BL21CodonPlus induced by CE6 phage.

B) EXPRESSION OF P501S IN BACULOVIRUS

5 The Bac-to-Bac baculovirus expression system (BRL Life Technologies, Inc.) was used to express P501S protein in insect cells. Full-length P501S (SEQ ID NO: 113) was amplified by PCR and cloned into the XbaI site of the donor plasmid pFastBacI. The recombinant bacmid and baculovirus were prepared according to the manufacturer's instructions. The recombinant baculovirus was amplified in Sf9 cells and the high titer
10 viral stocks were utilized to infect High Five cells (Invitrogen) to make the recombinant protein. The identity of the full-length protein was confirmed by N-terminal sequencing of the recombinant protein and by Western blot analysis (Figure 7). Specifically, 0.6 million High Five cells in 6-well plates were infected with either the unrelated control virus BV/ECD_PD (lane 2), with recombinant baculovirus for P501S at different amounts or
15 MOIs (lanes 4-8), or were uninfected (lane 3). Cell lysates were run on SDS-PAGE under reducing conditions and analyzed by Western blot with the anti-P501S monoclonal antibody P501S-10E3-G4D3 (prepared as described below). Lane 1 is the biotinylated protein molecular weight marker (BioLabs).

20 The localization of recombinant P501S in the insect cells was investigated as follows. The insect cells overexpressing P501S were fractionated into fractions of nucleus, mitochondria, membrane and cytosol. Equal amounts of protein from each fraction were analyzed by Western blot with a monoclonal antibody against P501S. Due to the scheme of fractionation, both nucleus and mitochondria fractions contain some plasma membrane components. However, the membrane fraction is basically free from
25 mitochondria and nucleus. P501S was found to be present in all fractions that contain the membrane component, suggesting that P501S may be associated with plasma membrane of the insect cells expressing the recombinant protein.

c) EXPRESSION OF P501S IN MAMMALIAN CELLS

Full-length P501S (553AA) was cloned into various mammalian expression vectors, including pCEP4 (Invitrogen), pVR1012 (Vical, San Diego, CA) and a modified form of the retroviral vector pBMN, referred to as pBIB. Transfection of P501S/pCEP4 and P501S/pVR1012 into HEK293 fibroblasts was carried out using the Fugene transfection reagent (Boehringer Mannheim). Briefly, 2 ul of Fugene reagent was diluted into 100 ul of serum-free media and incubated at room temperature for 5-10 min. This mixture was added to 1 ug of P501S plasmid DNA, mixed briefly and incubated for 30 minutes at room temperature. The Fugene/DNA mixture was added to cells and incubated for 24-48 hours. Expression of recombinant P501S in transfected HEK293 fibroblasts was detected by means of Western blot employing a monoclonal antibody to P501S.

Transfection of p501S/pCEP4 into CHO-K cells (American Type Culture Collection, Rockville, MD) was carried out using GenePorter transfection reagent (Gene Therapy Systems, San Diego, CA). Briefly, 15 μ l of GenePorter was diluted in 500 μ l of serum-free media and incubated at room temperature for 10 min. The GenePorter/media mixture was added to 2 μ g of plasmid DNA that was diluted in 500 μ l of serum-free media, mixed briefly and incubated for 30 min at room temperature. CHO-K cells were rinsed in PBS to remove serum proteins, and the GenePorter/DNA mix was added and incubated for 5 hours. The transfected cells were then fed an equal volume of 2x media and incubated for 24-48 hours.

FACS analysis of P501S transiently infected CHO-K cells, demonstrated surface expression of P501S. Expression was detected using rabbit polyclonal antisera raised against a P501S peptide, as described below. Flow cytometric analysis was performed using a FaCScan (Becton Dickinson), and the data were analyzed using the Cell Quest program.

EXAMPLE 18

PREPARATION AND CHARACTERIZATION OF ANTIBODIES
AGAINST PROSTATE-SPECIFIC POLYPEPTIDES5 A) **PREPARATION AND CHARACTERIZATION OF POLYCLONAL ANTIBODIES AGAINST
P703P, P504S AND P509S**

Polyclonal antibodies against P703P, P504S and P509S were prepared as follows.

Each prostate tumor antigen expressed in an *E. coli* recombinant expression system was grown overnight in LB broth with the appropriate antibiotics at 37°C in a shaking incubator. The next morning, 10 ml of the overnight culture was added to 500 ml to 2x YT plus appropriate antibiotics in a 2L-baffled Erlenmeyer flask. When the Optical Density (at 560 nm) of the culture reached 0.4-0.6, the cells were induced with IPTG (1 mM). Four hours after induction with IPTG, the cells were harvested by centrifugation. The cells were then washed with phosphate buffered saline and centrifuged again. The supernatant was discarded and the cells were either frozen for future use or immediately processed. Twenty ml of lysis buffer was added to the cell pellets and vortexed. To break open the *E. coli* cells, this mixture was then run through the French Press at a pressure of 16,000 psi. The cells were then centrifuged again and the supernatant and pellet were checked by SDS-PAGE for the partitioning of the recombinant protein. For proteins that localized to the cell pellet, the pellet was resuspended in 10 mM Tris pH 8.0, 1% CHAPS and the inclusion body pellet was washed and centrifuged again. This procedure was repeated twice more. The washed inclusion body pellet was solubilized with either 8 M urea or 6 M guanidine HCl containing 10 mM Tris pH 8.0 plus 10 mM imidazole. The solubilized protein was added to 5 ml of nickel-chelate resin (Qiagen) and incubated for 45 min to 1 hour at room temperature with continuous agitation. After incubation, the resin and protein mixture were poured through a disposable column and the flow through was collected. The column was then washed with 10-20 column volumes of the solubilization

buffer. The antigen was then eluted from the column using 8M urea, 10 mM Tris pH 8.0 and 300 mM imidazole and collected in 3 ml fractions. A SDS-PAGE gel was run to determine which fractions to pool for further purification.

As a final purification step, a strong anion exchange resin such as HiPrepQ
5 (Biorad) was equilibrated with the appropriate buffer and the pooled fractions from above were loaded onto the column. Each antigen was eluted off the column with a increasing salt gradient. Fractions were collected as the column was run and another SDS-PAGE gel was run to determine which fractions from the column to pool. The pooled fractions were dialyzed against 10 mM Tris pH 8.0. The proteins were then vialled after filtration through
10 a 0.22 micron filter and the antigens were frozen until needed for immunization.

Four hundred micrograms of each prostate antigen was combined with 100 micrograms of muramyl dipeptide (MDP). Every four weeks rabbits were boosted with 100 micrograms mixed with an equal volume of Incomplete Freund's Adjuvant (IFA). Seven days following each boost, the animal was bled. Sera was generated by incubating the
15 blood at 4°C for 12-4 hours followed by centrifugation.

Ninety-six well plates were coated with antigen by incubating with 50 microliters (typically 1 microgram) of recombinant protein at 4 °C for 20 hours. 250 microliters of BSA blocking buffer was added to the wells and incubated at room temperature for 2 hours. Plates were washed 6 times with PBS/0.01% Tween. Rabbit sera
20 was diluted in PBS. Fifty microliters of diluted sera was added to each well and incubated at room temperature for 30 min. Plates were washed as described above before 50 microliters of goat anti-rabbit horse radish peroxidase (HRP) at a 1:10000 dilution was added and incubated at room temperature for 30 min. Plates were again washed as described above and 100 microliters of TMB micowell peroxidase substrate was added to
25 each well. Following a 15 min incubation in the dark at room temperature, the colorimetric reaction was stopped with 100 microliters of 1N H₂SO₄ and read immediately at 450 nm. All polyclonal antibodies showed immunoreactivity to the appropriate antigen.

B) PREPARATION AND CHARACTERIZATION OF ANTIBODIES AGAINST P501S

A murine monoclonal antibody directed against the carboxy-terminus of the prostate-specific antigen P501S was prepared as follows.

A truncated fragment of P501S (amino acids 355-526 of SEQ ID NO: 113) 5 was generated and cloned into the pET28b vector (Novagen) and expressed in *E. coli* as a thioredoxin fusion protein with a histidine tag. The trx-P501S fusion protein was purified by nickel chromatography, digested with thrombin to remove the trx fragment and further purified by an acid precipitation procedure followed by reverse phase HPLC.

Mice were immunized with truncated P501S protein. Serum bleeds from 10 mice that potentially contained anti-P501S polyclonal sera were tested for P501S-specific reactivity using ELISA assays with purified P501S and trx-P501S proteins. Serum bleeds that appeared to react specifically with P501S were then screened for P501S reactivity by Western analysis. Mice that contained a P501S-specific antibody component were sacrificed and spleen cells were used to generate anti-P501S antibody producing 15 hybridomas using standard techniques. Hybridoma supernatants were tested for P501S-specific reactivity initially by ELISA, and subsequently by FACS analysis of reactivity with P501S transduced cells. Based on these results, a monoclonal hybridoma referred to as 10E3 was chosen for further subcloning. A number of subclones were generated, tested for specific reactivity to P501S using ELISA and typed for IgG isotype. The results of this 20 analysis are shown below in Table V. Of the 16 subclones tested, the monoclonal antibody 10E3-G4-D3 was selected for further study.

Table V
Isotype analysis of murine anti-P501S monoclonal antibodies

25

Hybridoma clone	Isotype	Estimated [Ig] in supernatant ($\mu\text{g/ml}$)
4D11	IgG1	14.6
1G1	IgG1	0.6
4F6	IgG1	72
4H5	IgG1	13.8
4H5-E12	IgG1	10.7

Hybridoma clone	Isotype	Estimated [Ig] in supernatant (μg/ml)
4H5-EH2	IgG1	9.2
4H5-H2-A10	IgG1	10
4H5-H2-A3	IgG1	12.8
4H5-H2-A10-G6	IgG1	13.6
4H5-H2-B11	IgG1	12.3
10E3	IgG2a	3.4
10E3-D4	IgG2a	3.8
10E3-D4-G3	IgG2a	9.5
10E3-D4-G6	IgG2a	10.4
10E3-E7	IgG2a	6.5
8H12	IgG2a	0.6

The specificity of 10E3-G4-D3 for P501S was examined by FACS analysis. Specifically, cells were fixed (2% formaldehyde, 10 minutes), permeabilized (0.1% saponin, 10 minutes) and stained with 10E3-G4-D3 at 0.5 – 1 μg/ml, followed by 5 incubation with a secondary, FITC-conjugated goat anti-mouse Ig antibody (Pharmingen, San Diego, CA). Cells were then analyzed for FITC fluorescence using an Excalibur fluorescence activated cell sorter. For FACS analysis of transduced cells, B-LCL were retrovirally transduced with P501S. For analysis of infected cells, B-LCL were infected with a vaccinia vector that expresses P501S. To demonstrate specificity in these assays, B-10 LCL transduced with a different antigen (P703P) and uninfected B-LCL vectors were utilized. 10E3-G4-D3 was shown to bind with P501S-transduced B-LCL and also with P501S-infected B-LCL, but not with either uninfected cells or P703P-transduced cells.

To determine whether the epitope recognized by 10E3-G4-D3 was found on the surface or in an intracellular compartment of cells, B-LCL were transduced with P501S 15 or HLA-B8 as a control antigen and either fixed and permeabilized as described above or directly stained with 10E3-G4-D3 and analyzed as above. Specific recognition of P501S by 10E3-G4-D3 was found to require permeabilization, suggesting that the epitope recognized by this antibody is intracellular.

The reactivity of 10E3-G4-D3 with the three prostate tumor cell lines 20 Lncap, PC-3 and DU-145, which are known to express high, medium and very low levels of P501S, respectively, was examined by permeabilizing the cells and treating them as

described above. Higher reactivity of 10E3-G4-D3 was seen with Lncap than with PC-3, which in turn showed higher reactivity than DU-145. These results are in agreement with the real time PCR and demonstrate that the antibody specifically recognizes P501S in these tumor cell lines and that the epitope recognized in prostate tumor cell lines is also 5 intracellular.

Specificity of 10E3-G4-D3 for P501S was also demonstrated by Western blot analysis. Lysates from the prostate tumor cell lines Lncap, DU-145 and PC-3, from 10 P501S-transiently transfected HEK293 cells, and from non-transfected HEK293 cells were generated. Western blot analysis of these lysates with 10E3-G4-D3 revealed a 46 kDa immunoreactive band in Lncap, PC-3 and P501S-transfected HEK cells, but not in DU-145 cells or non-transfected HEK293 cells. P501S mRNA expression is consistent with these 15 results since semi-quantitative PCR analysis revealed that P501S mRNA is expressed in Lncap, to a lesser but detectable level in PC-3 and not at all in DU-145 cells. Bacterially expressed and purified recombinant P501S (referred to as P501SStr2) was recognized by 15 10E3-G4-D3 (24 kDa), as was full-length P501S that was transiently expressed in HEK293 cells using either the expression vector VR1012 or pCEP4. Although the predicted molecular weight of P501S is 60.5 kDa, both transfected and “native” P501S run at a slightly lower mobility due to its hydrophobic nature.

Immunohistochemical analysis was performed on prostate tumor and a 20 panel of normal tissue sections (prostate, adrenal, breast, cervix, colon, duodenum, gall bladder, ileum, kidney, ovary, pancreas, parotid gland, skeletal muscle, spleen and testis). Tissue samples were fixed in formalin solution for 24 hours and embedded in paraffin before being sliced into 10 micron sections. Tissue sections were permeabilized and 25 incubated with 10E3-G4-D3 antibody for 1 hr. HRP-labeled anti-mouse followed by incubation with DAB chromogen was used to visualize P501S immunoreactivity. P501S was found to be highly expressed in both normal prostate and prostate tumor tissue but was not detected in any of the other tissues tested.

To identify the epitope recognized by 10E3-G4-D3, an epitope mapping approach was pursued. A series of 13 overlapping 20-21 mers (5 amino acid overlap; SEQ

ID NO: 489-501) was synthesized that spanned the fragment of P501S used to generate 10E3-G4-D3. Flat bottom 96 well microtiter plates were coated with either the peptides or the P501S fragment used to immunize mice, at 1 microgram/ml for 2 hours at 37 °C. Wells were then aspirated and blocked with phosphate buffered saline containing 1% (w/v) BSA
5 for 2 hours at room temperature, and subsequently washed in PBS containing 0.1% Tween 20 (PBST). Purified antibody 10E3-G4-D3 was added at 2 fold dilutions (1000 ng – 16 ng) in PBST and incubated for 30 minutes at room temperature. This was followed by washing 6 times with PBST and subsequently incubating with HRP-conjugated donkey anti-mouse IgG (H+L)Affinipure F(ab') fragment (Jackson Immunoresearch, West Grove, PA) at
10 1:20000 for 30 minutes. Plates were then washed and incubated for 15 minutes in tetramethyl benzidine. Reactions were stopped by the addition of 1N sulfuric acid and plates were read at 450 nm using an ELISA plate reader. As shown in Fig. 8, reactivity was seen with the peptide of SEQ ID NO: 496 (corresponding to amino acids 439-459 of P501S) and with the P501S fragment but not with the remaining peptides, demonstrating
15 that the epitope recognized by 10E3-G4-D3 is localized to amino acids 439-459 of SEQ ID NO: 113.

In order to further evaluate the tissue specificity of P501S, multi-array immunohistochemical analysis was performed on approximately 4700 different human tissues encompassing all the major normal organs as well as neoplasias derived from these
20 tissues. Sixty-five of these human tissue samples were of prostate origin. Tissue sections 0.6 mm in diameter were formalin-fixed and paraffin embedded. Samples were pretreated with HIER using 10 mM citrate buffer pH 6.0 and boiling for 10 min. Sections were stained with 10E3-G4-D3 and P501S immunoreactivity was visualized with HRP. All the 65 prostate tissues samples (5 normal, 55 untreated prostate tumors, 5 hormone refractory
25 prostate tumors) were positive, showing distinct perinuclear staining. All other tissues examined were negative for P501S expression.

C) PREPARATION AND CHARACTERIZATION OF ANTIBODIES AGAINST P503S

A fragment of P503S (amino acids 113-241 of SEQ ID NO: 114) was expressed and purified from bacteria essentially as described above for P501S and used to immunize both rabbits and mice. Mouse monoclonal antibodies were isolated using standard hybridoma technology as described above. Rabbit monoclonal antibodies were isolated using Selected Lymphocyte Antibody Method (SLAM) technology at Immgenics Pharmaceuticals (Vancouver, BC, Canada). Table VI, below, lists the monoclonal antibodies that were developed against P503S.

10

Table VI

Antibody	Species
20D4	Rabbit
JA1	Rabbit
1A4	Mouse
1C3	Mouse
1C9	Mouse
1D12	Mouse
2A11	Mouse
2H9	Mouse
4H7	Mouse
8A8	Mouse
8D10	Mouse
9C12	Mouse
6D12	Mouse

The DNA sequences encoding the complementarity determining regions (CDRs) for the rabbit monoclonal antibodies 20D4 and JA1 were determined and are provided in SEQ ID NO: 502 and 503, respectively.

In order to better define the epitope binding region of each of the antibodies, a series of overlapping peptides were generated that span amino acids 109-213 of SEQ ID NO: 114. These peptides were used to epitope map the anti-P503S monoclonal antibodies by ELISA as follows. The recombinant fragment of P503S that was employed as the

immunogen was used as a positive control. Ninety-six well microtiter plates were coated with either peptide or recombinant antigen at 20 ng/well overnight at 4 °C. Plates were aspirated and blocked with phosphate buffered saline containing 1% (w/v) BSA for 2 hours at room temperature then washed in PBS containing 0.1% Tween 20 (PBST). Purified 5 rabbit monoclonal antibodies diluted in PBST were added to the wells and incubated for 30 min at room temperature. This was followed by washing 6 times with PBST and incubation with Protein-A HRP conjugate at a 1:2000 dilution for a further 30 min. Plates were washed six times in PBST and incubated with tetramethylbenzidine (TMB) substrate 10 for a further 15 min. The reaction was stopped by the addition of 1N sulfuric acid and plates were read at 450 nm using at ELISA plate reader. ELISA with the mouse monoclonal antibodies was performed with supernatants from tissue culture run neat in the assay.

All of the antibodies bound to the recombinant P503S fragment, with the exception of the negative control SP2 supernatant. 20D4, JA1 and 1D12 bound strictly to 15 peptide #2101 (SEQ ID NO: 504), which corresponds to amino acids 151-169 of SEQ ID NO: 114. 1C3 bound to peptide #2102 (SEQ ID NO: 505), which corresponds to amino acids 165-184 of SEQ ID NO: 114. 9C12 bound to peptide #2099 (SEQ ID NO: 522), which corresponds to amino acids 120-139 of SEQ ID NO: 114. The other antibodies bind to regions that were not examined in these studies.

20 Subsequent to epitope mapping, the antibodies were tested by FACS analysis on a cell line that stably expressed P503S to confirm that the antibodies bind to cell surface epitopes. Cells stably transfected with a control plasmid were employed as a negative control. Cells were stained live with no fixative. 0.5 ug of anti-P503S monoclonal antibody was added and cells were incubated on ice for 30 min before being 25 washed twice and incubated with a FITC-labelled goat anti-rabbit or mouse secondary antibody for 20 min. After being washed twice, cells were analyzed with an Excalibur fluorescent activated cell sorter. The monoclonal antibodies 1C3, 1D12, 9C12, 20D4 and JA1, but not 8D3, were found to bind to a cell surface epitope of P503S.

In order to determine which tissues express P503S, immunohistochemical analysis was performed, essentially as described above, on a panel of normal tissues (prostate, adrenal, breast, cervix, colon, duodenum, gall bladder, ileum, kidney, ovary, pancreas, parotid gland, skeletal muscle, spleen and testis). HRP-labeled anti-mouse or 5 anti-rabbit antibody followed by incubation with TMB was used to visualize P503S immunoreactivity. P503S was found to be highly expressed in prostate tissue, with lower levels of expression being observed in cervix, colon, ileum and kidney, and no expression being observed in adrenal, breast, duodenum, gall bladder, ovary, pancreas, parotid gland, skeletal muscle, spleen and testis.

10 Western blot analysis was used to characterize anti-P503S monoclonal antibody specificity. SDS-PAGE was performed on recombinant (rec) P503S expressed in and purified from bacteria and on lysates from HEK293 cells transfected with full length P503S. Protein was transferred to nitrocellulose and then Western blotted with each of the anti-P503S monoclonal antibodies (20D4, JA1, 1D12, 6D12 and 9C12) at an antibody concentration of 1 ug/ml. Protein was detected using horse radish peroxidase (HRP) conjugated to either a goat anti-mouse monoclonal antibody or to protein A-sepharose. 15 The monoclonal antibody 20D4 detected the appropriate molecular weight 14 kDa recombinant P503S (amino acids 113-241) and the 23.5 kDa species in the HEK293 cell lysates transfected with full length P503S. Other anti-P503S monoclonal antibodies displayed similar specificity by Western blot.

d) PREPARATION AND CHARACTERIZATION OF ANTIBODIES AGAINST P703P

Rabbits were immunized with either a truncated (P703Ptr1; SEQ ID NO: 172) or full-length mature form (P703Pfl; SEQ ID NO: 523) of recombinant P703P protein was expressed in and purified from bacteria as described above. Affinity purified 25 polyclonal antibody was generated using immunogen P703Pfl or P703Ptr1 attached to a solid support. Rabbit monoclonal antibodies were isolated using SLAM technology at Immgenics Pharmaceuticals. Table VII below lists both the polyclonal and monoclonal antibodies that were generated against P703P.

Table VII

Antibody	Immunogen	Species/type
Aff. Purif. P703P (truncated); #2594	P703Ptrl	Rabbit polyclonal
Aff. Purif. P703P (full length); #9245	P703Pfl	Rabbit polyclonal
2D4	P703Ptrl	Rabbit monoclonal
8H2	P703Ptrl	Rabbit monoclonal
7H8	P703Ptrl	Rabbit monoclonal

5 The DNA sequences encoding the complementarity determining regions (CDRs) for the rabbit monoclonal antibodies 8H2, 7H8 and 2D4 were determined and are provided in SEQ ID NO: 506-508, respectively.

Epitope mapping studies were performed as described above. Monoclonal antibodies 2D4 and 7H8 were found to specifically bind to the peptides of SEQ ID NO: 10 509 (corresponding to amino acids 145-159 of SEQ ID NO: 172) and SEQ ID NO: 510 (corresponding to amino acids 11-25 of SEQ ID NO: 172), respectively. The polyclonal antibody 2594 was found to bind to the peptides of SEQ ID NO: 511-514, with the polyclonal antibody 9427 binding to the peptides of SEQ ID NO: 515-517.

The specificity of the anti-P703P antibodies was determined by Western blot analysis as follows. SDS-PAGE was performed on (1) bacterially expressed recombinant antigen; (2) lysates of HEK293 cells and Ltk^{-/-} cells either untransfected or transfected with a plasmid expressing full length P703P; and (3) supernatant isolated from these cell cultures. Protein was transferred to nitrocellulose and then Western blotted using the anti-P703P polyclonal antibody #2594 at an antibody concentration of 1 ug/ml. Protein 20 was detected using horse radish peroxidase (HRP) conjugated to an anti-rabbit antibody. A 35 kDa immunoreactive band could be observed with recombinant P703P. Recombinant P703P runs at a slightly higher molecular weight since it is epitope tagged. In lysates and supernatants from cells transfected with full length P703P, a 30 kDa band corresponding to P703P was observed. To assure specificity, lysates from HEK293 cells stably transfected

with a control plasmid were also tested and were negative for P703P expression. Other anti-P703P antibodies showed similar results.

5 Immunohistochemical studies were performed as described above, using anti-P703P monoclonal antibody. P703P was found to be expressed at high levels in normal prostate and prostate tumor tissue but was not detectable in all other tissues tested (breast tumor, lung tumor and normal kidney).

EXAMPLE 19

CHARACTERIZATION OF CELL SURFACE EXPRESSION AND 10 CHROMOSOME LOCALIZATION OF THE PROSTATE-SPECIFIC ANTIGEN P501S

This example describes studies demonstrating that the prostate-specific antigen P501S is expressed on the surface of cells, together with studies to determine the probable chromosomal location of P501S.

15 The protein P501S (SEQ ID NO: 113) is predicted to have 11 transmembrane domains. Based on the discovery that the epitope recognized by the anti-P501S monoclonal antibody 10E3-G4-D3 (described above in Example 17) is intracellular, it was predicted that following transmembrane determinants would allow the prediction of extracellular domains of P501S. Fig. 9 is a schematic representation of the P501S protein
20 showing the predicted location of the transmembrane domains and the intracellular epitope described in Example 17. Underlined sequence represents the predicted transmembrane domains, bold sequence represents the predicted extracellular domains, and italicized sequence represents the predicted intracellular domains. Sequence that is both bold and underlined represents sequence employed to generate polyclonal rabbit serum. The
25 location of the transmembrane domains was predicted using HHMTOPO as described by Tusnady and Simon (Principles Governing Amino Acid Composition of Integral Membrane Proteins: Applications to Topology Prediction, *J. Mol. Biol.* 283:489-506, 1998).

Based on Fig. 9, the P501S domain flanked by the transmembrane domains corresponding to amino acids 274-295 and 323-342 is predicted to be extracellular. The peptide of SEQ ID NO: 518 corresponds to amino acids 306-320 of P501S and lies in the predicted extracellular domain. The peptide of SEQ ID NO: 519, which is identical to the 5 peptide of SEQ ID NO: 518 with the exception of the substitution of the histidine with an asparagine, was synthesized as described above. A Cys-Gly was added to the C-terminus of the peptide to facilitate conjugation to the carrier protein. Cleavage of the peptide from the solid support was carried out using the following cleavage mixture: trifluoroacetic acid:ethanediol:thioanisole:water:phenol (40:1:2:2:3). After cleaving for two hours, the 10 peptide was precipitated in cold ether. The peptide pellet was then dissolved in 10% v/v acetic acid and lyophilized prior to purification by C18 reverse phase hplc. A gradient of 5-60% acetonitrile (containing 0.05% TFA) in water (containing 0.05% TFA) was used to elute the peptide. The purity of the peptide was verified by hplc and mass spectrometry, and was determined to be >95%. The purified peptide was used to generate rabbit 15 polyclonal antisera as described above.

Surface expression of P501S was examined by FACS analysis. Cells were stained with the polyclonal anti-P501S peptide serum at 10 µg/ml, washed, incubated with a secondary FITC-conjugated goat anti-rabbit Ig antibody (ICN), washed and analyzed for FITC fluorescence using an Excalibur fluorescence activated cell sorter. For FACS 20 analysis of transduced cells, B-LCL were retrovirally transduced with P501S. To demonstrate specificity in these assays, B-LCL transduced with an irrelevant antigen (P703P) or nontransduced were stained in parallel. For FACS analysis of prostate tumor cell lines, Lncap, PC-3 and DU-145 were utilized. Prostate tumor cell lines were dissociated from tissue culture plates using cell dissociation medium and stained as above. 25 All samples were treated with propidium iodide (PI) prior to FACS analysis, and data was obtained from PI-excluding (*i.e.*, intact and non-permeabilized) cells. The rabbit polyclonal serum generated against the peptide of SEQ ID NO: 519 was shown to specifically recognize the surface of cells transduced to express P501S, demonstrating that the epitope recognized by the polyclonal serum is extracellular.

To determine biochemically if P501S is expressed on the cell surface, peripheral membranes from Lncap cells were isolated and subjected to Western blot analysis. Specifically, Lncap cells were lysed using a dounce homogenizer in 5 ml of homogenization buffer (250 mM sucrose, 10 mM HEPES, 1mM EDTA, pH 8.0, 1 5 complete protease inhibitor tablet (Boehringer Mannheim)). Lysate samples were spun at 1000 g for 5 min at 4 °C. The supernatant was then spun at 8000g for 10 min at 4 °C. Supernatant from the 8000g spin was recovered and subjected to a 100,000g spin for 30 min at 4 °C to recover peripheral membrane. Samples were then separated by SDS-PAGE and Western blotted with the mouse monoclonal antibody 10E3-G4-D3 (described above in 10 Example 17) using conditions described above. Recombinant purified P501S, as well as HEK293 cells transfected with and over-expressing P501S were included as positive controls for P501S detection. LCL cell lysate was included as a negative control. P501S could be detected in Lncap total cell lysate, the 8000g (internal membrane) fraction and also in the 100,000g (plasma membrane) fraction. These results indicate that P501S is 15 expressed at, and localizes to, the peripheral membrane.

To demonstrate that the rabbit polyclonal antiserum generated to the peptide of SEQ ID NO: 519 specifically recognizes this peptide as well as the corresponding native peptide of SEQ ID NO: 518, ELISA analyses were performed. For these analyses, flat-bottomed 96 well microtiter plates were coated with either the peptide of SEQ ID NO: 519, 20 the longer peptide of SEQ ID NO: 520 that spans the entire predicted extracellular domain, the peptide of SEQ ID NO: 521 which represents the epitope recognized by the P501S-specific antibody 10E3-G4-D3, or a P501S fragment (corresponding to amino acids 355-526 of SEQ ID NO: 113) that does not include the immunizing peptide sequence, at 1 µg/ml for 2 hours at 37 °C. Wells were aspirated, blocked with phosphate buffered saline 25 containing 1% (w/v) BSA for 2 hours at room temperature and subsequently washed in PBS containing 0.1% Tween 20 (PBST). Purified anti-P501S polyclonal rabbit serum was added at 2 fold dilutions (1000 ng - 125 ng) in PBST and incubated for 30 min at room temperature. This was followed by washing 6 times with PBST and incubating with HRP-conjugated goat anti-rabbit IgG (H+L) Affinipure F(ab') fragment at 1:20000 for 30 min.

Plates were then washed and incubated for 15 min in tetramethyl benzidine. Reactions were stopped by the addition of 1N sulfuric acid and plates were read at 450 nm using an ELISA plate reader. As shown in Fig. 11, the anti-P501S polyclonal rabbit serum specifically recognized the peptide of SEQ ID NO: 519 used in the immunization as well as 5 the longer peptide of SEQ ID NO: 520, but did not recognize the irrelevant P501S-derived peptides and fragments.

In further studies, rabbits were immunized with peptides derived from the P501S sequence and predicted to be either extracellular or intracellular, as shown in Fig. 9. Polyclonal rabbit sera were isolated and polyclonal antibodies in the serum were purified, 10 as described above. To determine specific reactivity with P501S, FACS analysis was employed, utilizing either B-LCL transduced with P501S or the irrelevant antigen P703P, of B-LCL infected with vaccinia virus-expressing P501S. For surface expression, dead and non-intact cells were excluded from the analysis as described above. For intracellular staining, cells were fixed and permeabilized as described above. Rabbit polyclonal serum 15 generated against the peptide of SEQ ID NO: 548, which corresponds to amino acids 181-198 of P501S, was found to recognize a surface epitope of P501S. Rabbit polyclonal serum generated against the peptide SEQ ID NO: 551, which corresponds to amino acids 543-553 of P501S, was found to recognize an epitope that was either potentially extracellular or intracellular since in different experiments intact or permeabilized cells 20 were recognized by the polyclonal sera. Based on similar deductive reasoning, the sequences of SEQ ID NO: 541-547, 549 and 550, which correspond to amino acids 109-122, 539-553, 509-520, 37-54, 342-359, 295-323, 217-274, 143-160 and 75-88, respectively, of P501S, can be considered to be potential surface epitopes of P501S 25 recognized by antibodies.

The chromosomal location of P501S was determined using the GeneBridge 4 Radiation Hybrid panel (Research Genetics). The PCR primers of SEQ ID NO: 528 and 529 were employed in PCR with DNA pools from the hybrid panel according to the manufacturer's directions. After 38 cycles of amplification, the reaction products were separated on a 1.2% agarose gel, and the results were analyzed through the Whitehead

Institute/MIT Center for Genome Research web server (<http://www-genome.wi.mit.edu/cgi-bin/contig/rhMapper.pl>) to determine the probable chromosomal location. Using this approach, P501S was mapped to the long arm of chromosome 1 at WI-9641 between q32 and q42. This region of chromosome 1 has been linked to prostate cancer susceptibility in hereditary prostate cancer (Smith *et al.* *Science* 274:1371-1374, 1996 and Berthon *et al.* *Am. J. Hum. Genet.* 62:1416-1424, 1998). These results suggest that P501S may play a role in prostate cancer malignancy.

EXAMPLE 20

10 REGULATION OF EXPRESSION OF THE PROSTATE-SPECIFIC ANTIGEN P501S

Steroid (androgen) hormone modulation is a common treatment modality in prostate cancer. The expression of a number of prostate tissue-specific antigens have previously been demonstrated to respond to androgen. The responsiveness of the prostate-specific antigen P501S to androgen treatment was examined in a tissue culture system as follows.

Cells from the prostate tumor cell line LNCaP were plated at 1.5×10^6 cells/T75 flask (for RNA isolation) or 3×10^5 cells/well of a 6-well plate (for FACS analysis) and grown overnight in RPMI 1640 media containing 10% charcoal-stripped fetal calf serum (BRL Life Technologies, Gaithersburg, MD). Cell culture was continued for an additional 72 hours in RPMI 1640 media containing 10% charcoal-stripped fetal calf serum, with 1 nM of the synthetic androgen Methyltrienolone (R1881; New England Nuclear) added at various time points. Cells were then harvested for RNA isolation and FACS analysis at 0, 1, 2, 4, 8, 16, 24, 28 and 72-hours post androgen addition. FACS analysis was performed using the anti-P501S antibody 10E3-G4-D3 and permeabilized cells.

For Northern analysis, 5-10 micrograms of total RNA was run on a formaldehyde denaturing gel, transferred to Hybond-N nylon membrane (Amersham Pharmacia Biotech, Piscataway, NJ), cross-linked and stained with methylene blue. The

filter was then prehybridized with Church's Buffer (250 mM Na₂HPO₄, 70 mM H₃PO₄, 1 mM EDTA, 1% SDS, 1% BSA in pH 7.2) at 65 °C for 1 hour. P501S DNA was labeled with ³²P using High Prime random-primed DNA labeling kit (Boehringer Mannheim). Unincorporated label was removed using MicroSpin S300-HR columns (Amersham 5 Pharmacia Biotech). The RNA filter was then hybridized with fresh Church's Buffer containing labeled cDNA overnight, washed with 1X SCP (0.1 M NaCl, 0.03 M Na₂HPO₄.7H₂O, 0.001 M Na₂EDTA), 1% sarkosyl (n-lauroylsarcosine) and exposed to X-ray film.

Using both FACS and Northern analysis, P501S message and protein levels 10 were found in increase in response to androgen treatment.

EXAMPLE 20

PREPARATION OF FUSION PROTEINS OF PROSTATE-SPECIFIC ANTIGENS

15 The example describes the preparation of a fusion protein of the prostate-specific antigen P703P and a truncated form of the known prostate antigen PSA. The truncated form of PSA has a 21 amino acid deletion around the active serine site. The expression construct for the fusion protein also has a restriction site at 3' end, immediately prior to the termination codon, to aid in adding cDNA for additional antigens.

20 The full-length cDNA for PSA was obtained by RT-PCR from a pool of RNA from human prostate tumor tissues using the primers of SEQ ID NO: 607 and 608, and cloned in the vector pCR-Blunt II-TOPO. The resulting cDNA was employed as a template to make two different fragments of PSA by PCR with two sets of primers (SEQ ID NO: 609 and 610; and SEQ ID NO: 611 and 612). The PCR products having the 25 expected size were used as templates to make truncated forms of PSA by PCR with the primers of SEQ ID NO: 611 and 613, which generated PSA (delta 208-218 in amino acids). The cDNA for the mature form of P703P with a 6X histidine tag at the 5' end, was prepared by PCR with P703P and the primers of SEQ ID NO: 614 and 615. The cDNA for the fusion of P703P with the truncated form of PSA (referred to as FOPP) was then

obtained by PCR using the modified P703P cDNA and the truncated form of PSA cDNA as templates and the primers of SEQ ID NO: 614 and 615. The FOPP cDNA was cloned into the NdeI site and XhoI site of the expression vector pCRX1, and confirmed by DNA sequencing. The determined cDNA sequence for the fusion construct FOPP is provided in
5 SEQ ID NO: 616, with the amino acid sequence being provided in SEQ ID NO: 617.

EXAMPLE 21

REAL-TIME PCR CHARACTERIZATION OF THE PROSTATE-SPECIFIC ANTIGEN P501S IN PERIPHERAL BLOOD OF PROSTATE CANCER PATIENTS

10

Circulating epithelial cells were isolated from fresh blood of normal individuals and metastatic prostate cancer patients, mRNA isolated and cDNA prepared using real-time PCR procedures. Real-time PCR was performed with the Taqman™ procedure using both gene specific primers and probes to determine the levels of gene
15 expression.

Epithelial cells were enriched from blood samples using an immunomagnetic bead separation method (Dynal A.S., Oslo, Norway). Isolated cells were lysed and the magnetic beads removed. The lysate was then processed for poly A+ mRNA isolation using magnetic beads coated with Oligo(dT)25. After washing the beads in
20 buffer, bead/poly A+ RNA samples were suspended in 10 mM Tris HCl pH 8.0 and subjected to reversed transcription. The resulting cDNA was subjected to real-time PCR using gene specific primers. Beta-actin content was also determined and used for normalization. Samples with P501S copies greater than the mean of the normal samples +
3 standard deviations were considered positive. Real time PCR on blood samples was
25 performed using the Taqman™ procedure but extending to 50 cycles using forward and reverse primers and probes specific for P501S. Of the eight samples tested, 6 were positive for P501S and β-actin signal. The remaining 2 samples had no detectable β-actin or P501S. No P501S signal was observed in the four normal blood samples tested.

From the foregoing, it will be appreciated that, although specific embodiments of the invention have been described herein for the purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the present invention is not limited except as by the appended claims.

CLAIMS

What is claimed:

1. An isolated polypeptide, comprising at least an immunogenic portion of a prostate-specific protein, wherein the protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(a) sequences recited in SEQ ID NO: 2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-361, 363-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471, 472-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-689, 691-698, 702-705, 709-772 and 779;

(b) sequences that hybridize to a sequence recited in any one of SEQ ID NOs: 2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-361, 363-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471, 472-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-689, 691-698, 702-705, 709-772 and 779 under moderately stringent conditions; and

(c) complements of sequences of (a) or (b).

2. An isolated polypeptide according to claim 1, wherein the polypeptide comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NO: 2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-361, 363-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434,

435, 442-444, 446, 450, 452, 453, 459-461, 468-471, 472-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-689, 691-698, 702-705, 709-772 and 779, or a complement of any of the foregoing polynucleotide sequences.

3. An isolated polypeptide comprising a sequence recited in any one of SEQ ID NO: 108, 112, 113, 114, 172, 176, 178, 327, 329, 331, 338, 339, 383, 477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568, 573-586, 588-590, 592, 706-708, 780, 781, 810, 811 and 814.

4. An isolated polynucleotide encoding at least 15 amino acid residues of a prostate-specific protein, or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with antigen-specific antisera is not substantially diminished, wherein the protein comprises an amino acid sequence that is encoded by a polynucleotide comprising a sequence recited in any one of SEQ ID NO: 2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-361, 363-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471, 472-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-689, 691-698, 702-705, 709-772 and 779, or a complement of any of the foregoing sequences.

5. An isolated polynucleotide encoding a prostate-specific protein, or a variant thereof, wherein the protein comprises an amino acid sequence that is encoded by a polynucleotide comprising a sequence recited in any one of SEQ ID NOs: 2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-361, 363-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-

461, 468-471, 472-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-689, 691-698, 702-705, 709-772 and 779, or a complement of any of the foregoing sequences.

6. An isolated polynucleotide, comprising a sequence recited in any one of SEQ ID NO: 2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-361, 363-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471, 472-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-689, 691-698, 702-705, 709-772 and 779.

7. An isolated polynucleotide, comprising a sequence that hybridizes to a sequence recited in any one of SEQ ID NO: 2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-361, 363-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471, 472-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-689, 691-698, 702-705, 709-772 and 779 under moderately stringent conditions.

8. An isolated polynucleotide complementary to a polynucleotide according to any one of claims 4-7.

9. An expression vector, comprising a polynucleotide according to any one of claims 4-8.

10. A host cell transformed or transfected with an expression vector according to claim 9.

11. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to a prostate-specific protein that comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NO: 2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-361, 363-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471, 472-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-689, 691-698, 702-705, 709-772 and 779, or a complement of any of the foregoing polynucleotide sequences.

12. A fusion protein, comprising at least one polypeptide according to claim 1.

13. A fusion protein according to claim 12, wherein the fusion protein comprises an expression enhancer that increases expression of the fusion protein in a host cell transfected with a polynucleotide encoding the fusion protein.

14. A fusion protein according to claim 12, wherein the fusion protein comprises a T helper epitope that is not present within the polypeptide of claim 1.

15. A fusion protein according to claim 12, wherein the fusion protein comprises an affinity tag.

16. An isolated polynucleotide encoding a fusion protein according to claim 12.

17. A pharmaceutical composition, comprising a physiologically acceptable carrier and at least one component selected from the group consisting of:

(a) a polypeptide according to claim 1;

- (b) a polynucleotide according to claim 4;
 - (c) an antibody according to claim 11;
 - (d) a fusion protein according to claim 12; and
 - (e) a polynucleotide according to claim 16.
18. An immunogenic composition comprising an immunostimulant and at least one component selected from the group consisting of:
- (a) a polypeptide according to claim 1;
 - (b) a polynucleotide according to claim 4;
 - (c) an antibody according to claim 11;
 - (d) a fusion protein according to claim 12; and
 - (e) a polynucleotide according to claim 16.
19. An immunogenic composition according to claim 18, wherein the immunostimulant is an adjuvant.
20. An immunogenic composition according to claim 18, wherein the immunostimulant induces a predominantly Type I response.
21. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a pharmaceutical composition according to claim 17.
22. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of an immunogenic composition according to claim 18.

23. A pharmaceutical composition comprising an antigen-presenting cell that expresses a polypeptide according to claim 1, in combination with a pharmaceutically acceptable carrier or excipient.

24. A pharmaceutical composition according to claim 23, wherein the antigen presenting cell is a dendritic cell or a macrophage.

25. An immunogenic composition comprising an antigen-presenting cell that expresses a polypeptide comprising at least an immunogenic portion of a prostate-specific protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(a) sequences recited in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777 and 789;

(b) sequences that hybridize to a sequence recited in any one of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777 and 789 under moderately stringent conditions; and

(c) complements of sequences of (i) or (ii);
in combination with an immunostimulant.

26. An immunogenic composition according to claim 25, wherein the immunostimulant is an adjuvant.

27. An immunogenic composition according to claim 25, wherein the immunostimulant induces a predominantly Type I response.

28. An immunogenic composition according to claim 25, wherein the antigen-presenting cell is a dendritic cell.

29. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of an antigen-presenting cell that expresses a polypeptide comprising at least an immunogenic portion of a prostate-specific protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(a) sequences recited in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777 and 789;

(b) sequences that hybridize to a sequence recited in any one of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777 and 789 under moderately stringent conditions; and

(c) complements of sequences of (i) or (ii) encoded by a polynucleotide recited in any one of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777 and 789;

and thereby inhibiting the development of a cancer in the patient.

30. A method according to claim 29, wherein the antigen-presenting cell is a dendritic cell.

31. A method according to any one of claims 21, 22 and 29, wherein the cancer is prostate cancer.

32. A method for removing tumor cells from a biological sample, comprising contacting a biological sample with T cells that specifically react with a prostate-specific protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(i) polynucleotides recited in any one of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777 and 789; and

(ii) complements of the foregoing polynucleotides;

wherein the step of contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the antigen from the sample.

33. A method according to claim 32, wherein the biological sample is blood or a fraction thereof.

34. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient a biological sample treated according to the method of claim 32.

35. A method for stimulating and/or expanding T cells specific for a prostate-specific protein, comprising contacting T cells with at least one component selected from the group consisting of:

(a) polypeptides comprising at least an immunogenic portion of a prostate-specific protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(i) sequences recited in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777 and 789;

(ii) sequences that hybridize to a sequence recited in any one of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777 and 789 under moderately stringent conditions; and

(iii) complements of sequences of (i) or (ii);

(b) polynucleotides encoding a polypeptide of (a); and
 (c) antigen presenting cells that express a polypeptide of (a);
 under conditions and for a time sufficient to permit the stimulation and/or
 expansion of T cells.

36. An isolated T cell population, comprising T cells prepared according to the method of claim 35.

37. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a T cell population according to claim 36.

38. A method for inhibiting the development of a cancer in a patient, comprising the steps of:

- (a) incubating CD4⁺ and/or CD8⁺ T cells isolated from a patient with at least one component selected from the group consisting of:
 - (i) polypeptides comprising at least an immunogenic portion of a prostate-specific protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:
 - (1) sequences recited in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777 and 789;
 - (2) sequences that hybridize to a sequence recited in any one of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777 and 789 under moderately stringent conditions; and
 - (3) complements of sequences of (1) or (2);
 - (ii) polynucleotides encoding a polypeptide of (i); and
 - (iii) antigen presenting cells that expresses a polypeptide of (i);

such that T cells proliferate; and

- (b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of a cancer in the patient.

39. A method for inhibiting the development of a cancer in a patient, comprising the steps of:

- (a) incubating CD4⁺ and/or CD8+ T cells isolated from a patient with at least one component selected from the group consisting of:

(i) polypeptides comprising at least an immunogenic portion of a prostate-specific protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(1) sequences recited in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777 and 789;

(2) sequences that hybridize to a sequence recited in any one of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777 and 789 under moderately stringent conditions; and

(3) complements of sequences of (1) or (2);

(ii) polynucleotides encoding a polypeptide of (i); and

(iii) antigen presenting cells that express a polypeptide of (i);

such that T cells proliferate;

(b) cloning at least one proliferated cell to provide cloned T cells; and

(c) administering to the patient an effective amount of the cloned T cells, and thereby inhibiting the development of a cancer in the patient.

40. A method for determining the presence or absence of a cancer in a patient, comprising the steps of:

- (a) contacting a biological sample obtained from a patient with a binding agent that binds to a prostate-specific protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777 and 789 or a complement of any of the foregoing polynucleotide sequences;
- (b) detecting in the sample an amount of polypeptide that binds to the binding agent; and
- (c) comparing the amount of polypeptide to a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient.

41. A method according to claim 40, wherein the binding agent is an antibody.
42. A method according to claim 43, wherein the antibody is a monoclonal antibody.
43. A method according to claim 40, wherein the cancer is prostate cancer.
44. A method for monitoring the progression of a cancer in a patient, comprising the steps of:

- (a) contacting a biological sample obtained from a patient at a first point in time with a binding agent that binds to a prostate-specific protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777 and 789 or a complement of any of the foregoing polynucleotide sequences;
- (b) detecting in the sample an amount of polypeptide that binds to the binding agent;

(c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and

(d) comparing the amount of polypeptide detected in step (c) to the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

45. A method according to claim 44, wherein the binding agent is an antibody.

46. A method according to claim 45, wherein the antibody is a monoclonal antibody.

47. A method according to claim 44, wherein the cancer is a prostate cancer.

48. A method for determining the presence or absence of a cancer in a patient, comprising the steps of:

(a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a prostate-specific protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777 and 789, or a complement of any of the foregoing polynucleotide sequences;

(b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; and

(c) comparing the amount of polynucleotide that hybridizes to the oligonucleotide to a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient.

49. A method according to claim 48, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a polymerase chain reaction.

50. A method according to claim 48, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a hybridization assay.

51. A method for monitoring the progression of a cancer in a patient, comprising the steps of:

(a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a prostate-specific protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777 and 789, or a complement of any of the foregoing polynucleotide sequences;

(b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide;

(c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and

(d) comparing the amount of polynucleotide detected in step (c) to the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

52. A method according to claim 51, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a polymerase chain reaction.

53. A method according to claim 51, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a hybridization assay.

54. A diagnostic kit, comprising:

- (a) one or more antibodies according to claim 11; and
- (b) a detection reagent comprising a reporter group.

55. A kit according to claim 54, wherein the antibodies are immobilized on a solid support.

56. A kit according to claim 54, wherein the detection reagent comprises an anti-immunoglobulin, protein G, protein A or lectin.

57. A kit according to claim 54, wherein the reporter group is selected from the group consisting of radioisotopes, fluorescent groups, luminescent groups, enzymes, biotin and dye particles.

58. An oligonucleotide comprising 10 to 40 contiguous nucleotides that hybridize under moderately stringent conditions to a polynucleotide that encodes a prostate-specific protein, wherein the protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NO: 2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-361, 363-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471, 472-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-689, 691-698, 702-705, 709-772 and 779, or a complement of any of the foregoing polynucleotides.

59. A oligonucleotide according to claim 58, wherein the oligonucleotide comprises 10-40 contiguous nucleotides recited in any one of SEQ ID NO: 2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-361, 363-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471, 472-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-689, 691-698, 702-705, 709-772 and 779.

60. A diagnostic kit, comprising:
 - (a) an oligonucleotide according to claim 59; and
 - (b) a diagnostic reagent for use in a polymerase chain reaction or hybridization assay.

COMPOSITIONS AND METHODS FOR THE THERAPY
AND DIAGNOSIS OF PROSTATE CANCER

ABSTRACT OF THE DISCLOSURE

Compositions and methods for the therapy and diagnosis of cancer, such as prostate cancer, are disclosed. Compositions may comprise one or more prostate-specific proteins, immunogenic portions thereof, or polynucleotides that encode such portions. Alternatively, a therapeutic composition may comprise an antigen presenting cell that expresses a prostate-specific protein, or a T cell that is specific for cells expressing such a protein. Such compositions may be used, for example, for the prevention and treatment of diseases such as prostate cancer. Diagnostic methods based on detecting a prostate-specific protein, or mRNA encoding such a protein, in a sample are also provided.

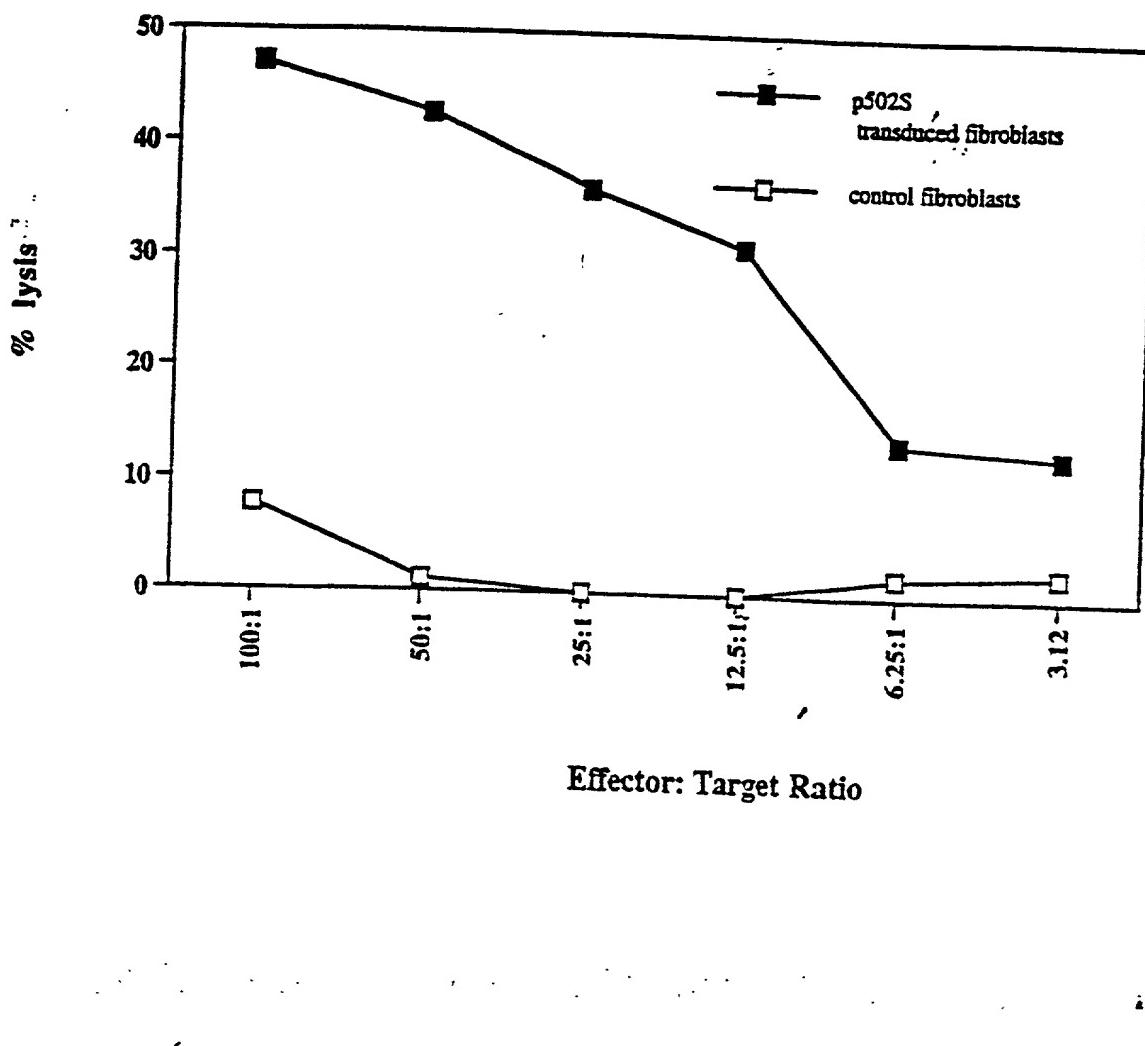


FIG. 1

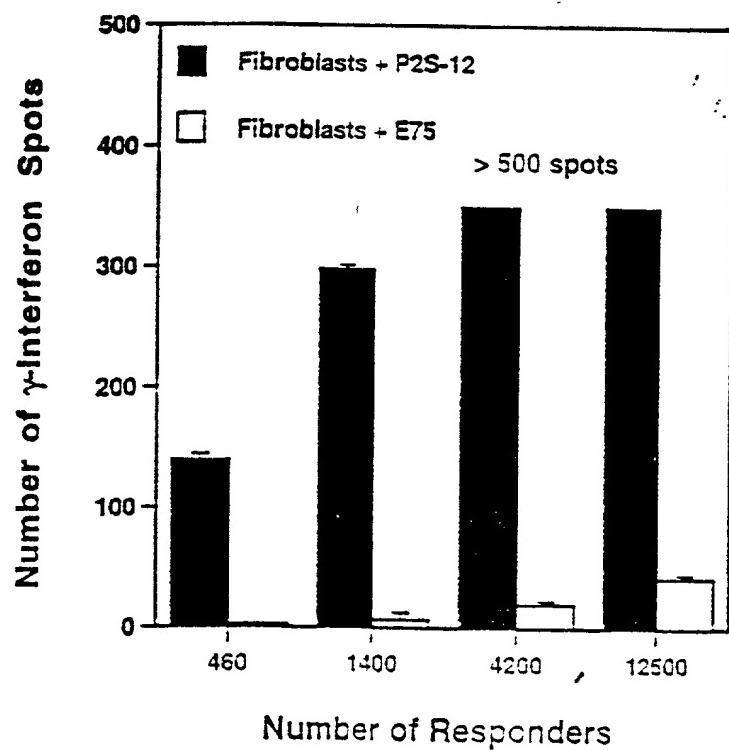


FIG. 2A

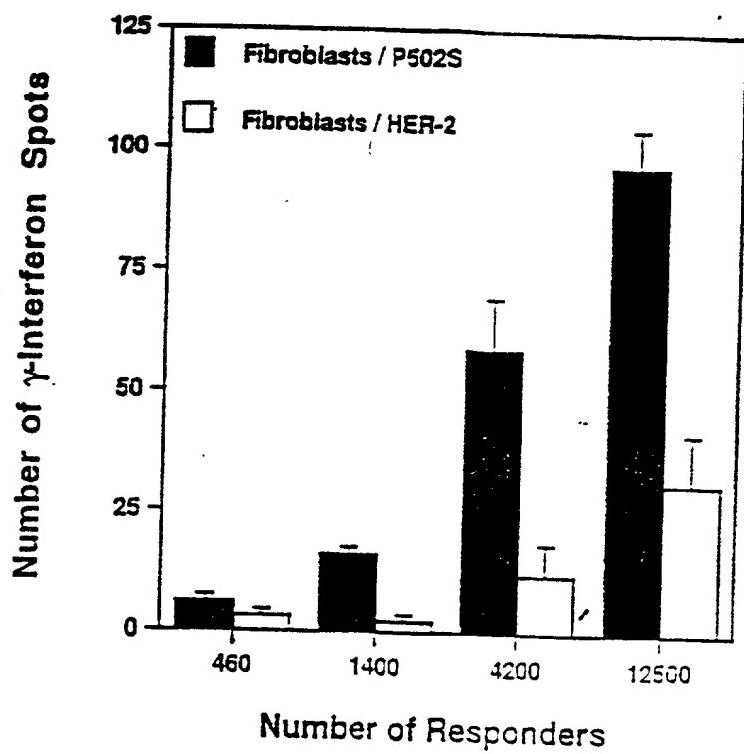


FIG. 2B

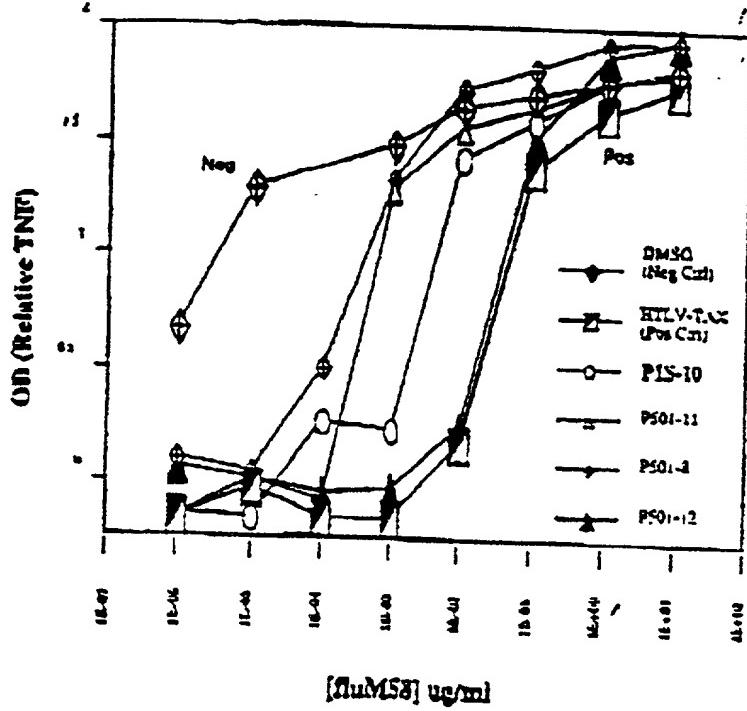


Figure 3

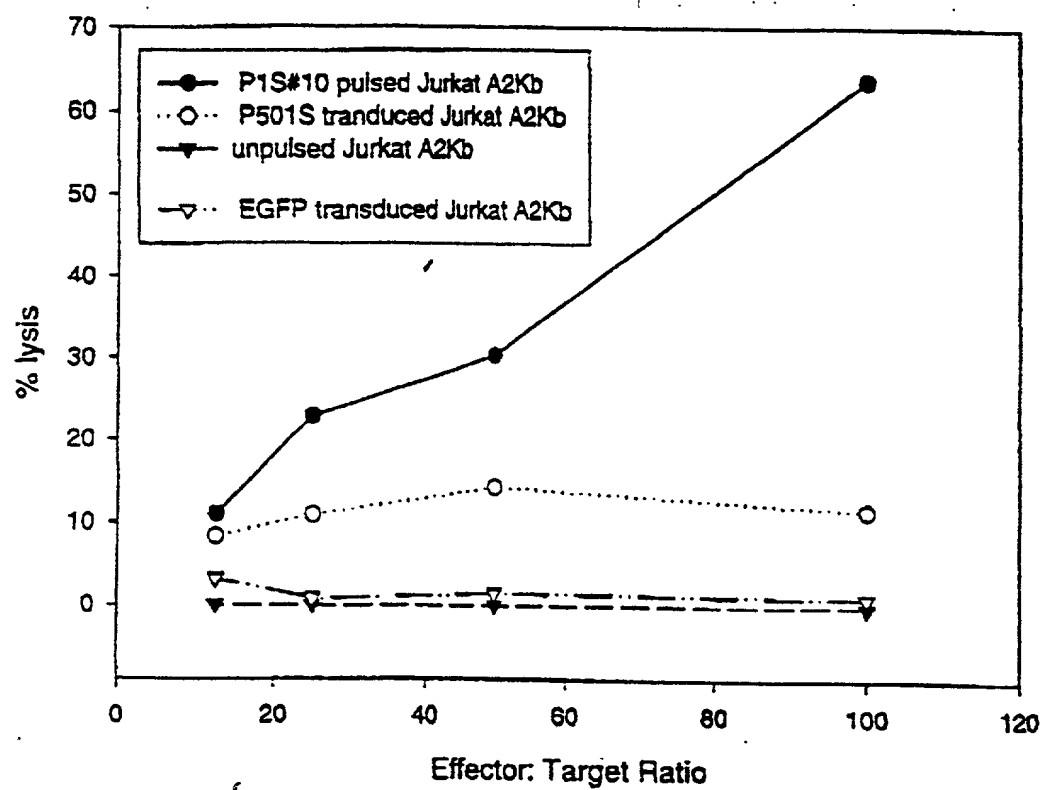


Figure 4

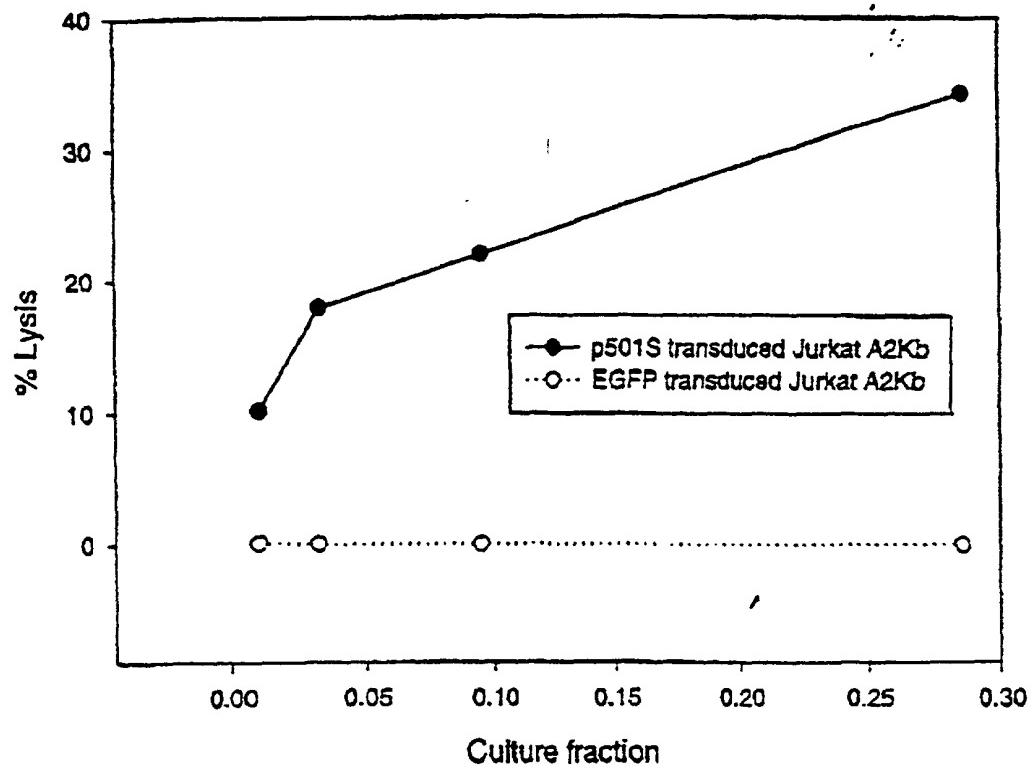


Figure 5

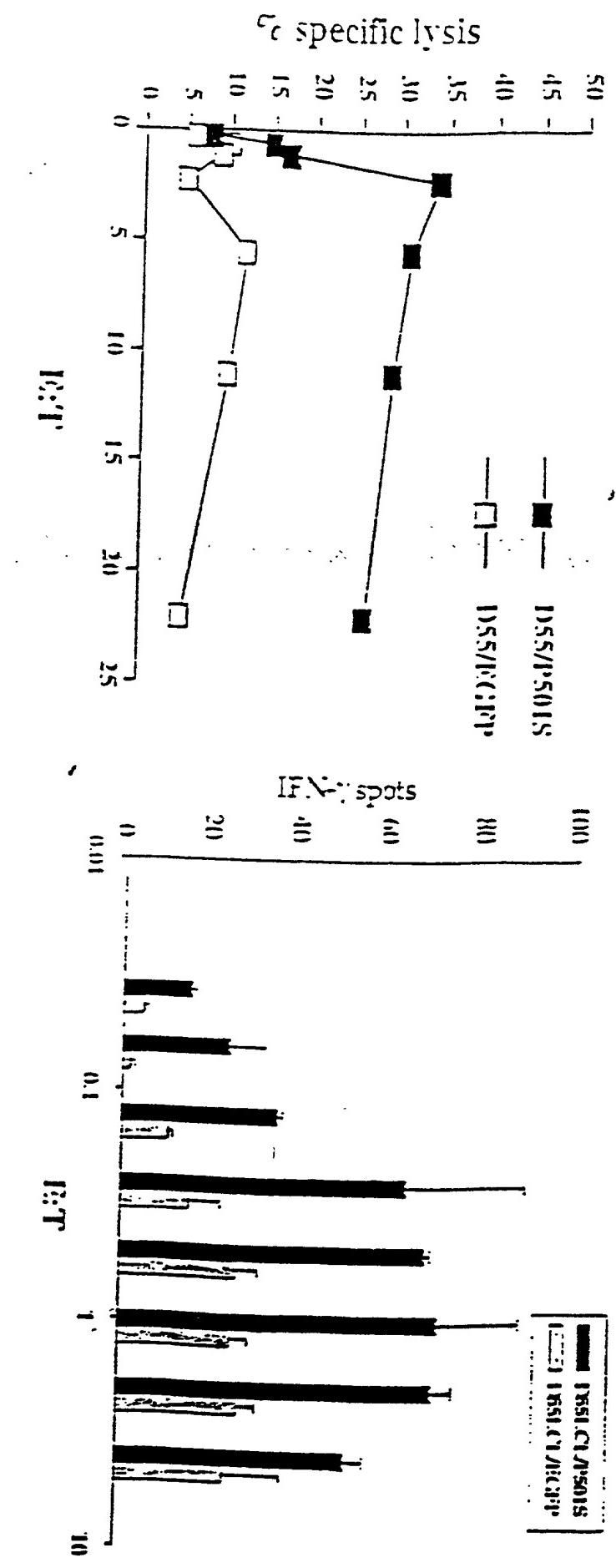
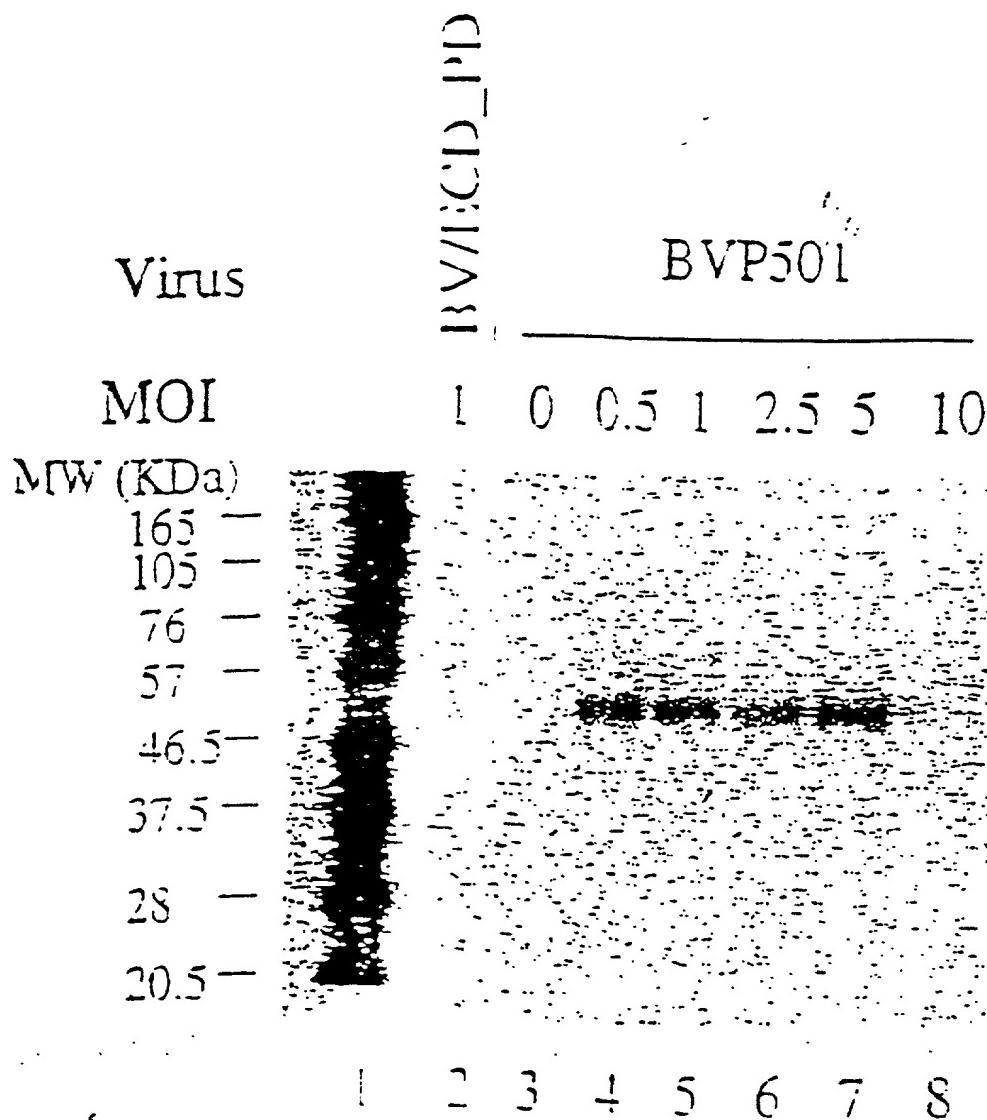


Fig. 6A

Fig. 6B

Expression of P501S
by the Baculovirus Expression System

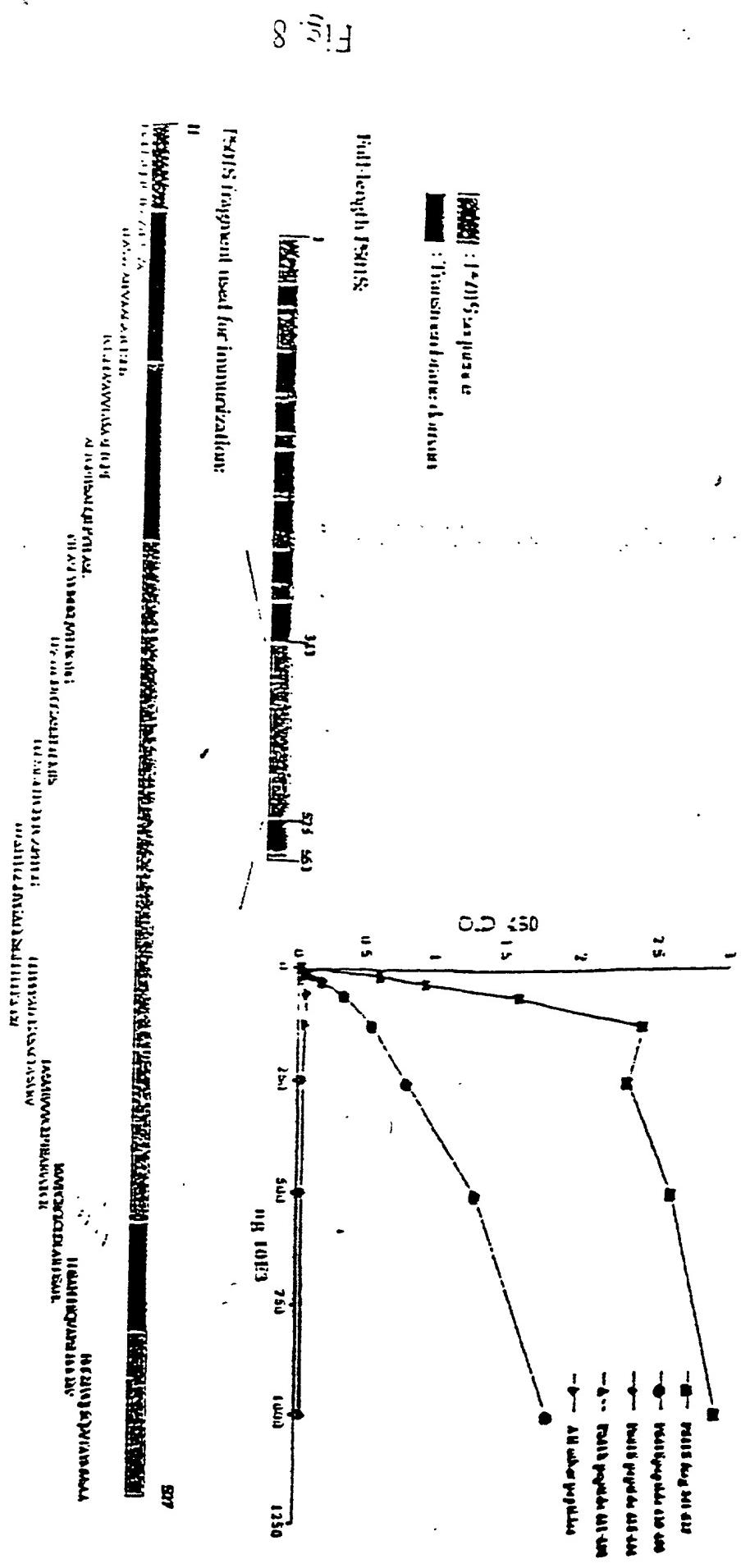


0.6 million μ g/ml of 293T cells in a 12-well plate were infected with an unrelated control virus BVECD_P0 or with recombinant baculovirus for P501 at different MOIs (lane 4 - 8). Cell lysates were run on SDS-PAGE under the reducing condition and analyzed by Western blot with a monoclonal antibody against the protein molecular weight marker.

Cells in a 12-well plate were infected with an unrelated control virus (lane 3), or with recombinant baculovirus for P501 (lane 4 - 8). Cell lysates were run on SDS-PAGE under the reducing condition and analyzed by Western blot with a monoclonal antibody against the protein molecular weight marker. Lane 1 is the biotinylated protein.

Fig. 7

Figure 8. Mapping of the epitope recognized by
10E3-G4-D3



7

Figure 1. Schematic of P501S with predicted transmembrane, cytoplasmic, and extracellular regions

Underlined sequence: Predicted transmembrane domain; *Bold sequence:* Predicted extracellular domain;
Italic sequence: Predicted intracellular domain. Sequence in bold/batched line: used to generate polyclonal rabbit serum

P501S **AQDLYVNLLTQIYCTAACRIVVPIIILFECVCEKIKWTRVYQIQLVYCYPILLAS**
DWWRGIRWIRRPP **EWYALSLQHLSLHPRACWYL** **AGLICPPIPPLF** **IATIILQYQLLDRCQYCPYL**
PAUSSUERPPDPPC **AYSVYAMMIGCICVIVIIPAI** **DWYISVATAPVTCRQEV**
QIQTATIIFLTCEYAVIILY **AKFIAAICRPAACTTSRVSQHICP** **RAIAAFRMCAATIPTI.**
MDPCTTAAPPTTAAK **LIVYAHICQYWMAI** **MIIITIPTVTP** **VCTGTLIYQGIVVPIIAPPGTEARHUYHPCVW**
MSYLLMFLQCAISLYVSIYVM **DRIVQHFCCTRAVWAS** **YAAIIPVAACTATLSHSYAYTA** **SAA**
ITGIFTSAQOLPPYTLASLY **IREKQVFIIPKVRGCGASSDSI** **MTSTIJCOPKPGAPPNGIVGAGSII.**
IPPPPPATCGASA **CDVSVVRRVWVWPPTRAEVVPSCG** **ICLTHAIIIDSATISSLQVAPSII** **MGSIIVQIISQS**
VTA **YMMVSSAAGLGLVALYFAT** **QVVFKPSDIAKYSAA**

Underlined sequence: Predicted transmembrane domain; *Bold sequence:* Predicted extracellular domain;
Italic sequence: Predicted intracellular domain. Sequence in bold/batched line: used to generate polyclonal rabbit serum

Localization of domains predicted using IIMMTOPI (G.P. Tushnay and L. Simon (1998) Principles Governing Amino Acid Composition of Integral Membrane Proteins: Applications to topology prediction. *J. Mol. Biol.* 283, 489-506.

Genomic Map of (S) *Catlxa* Candidate Genes

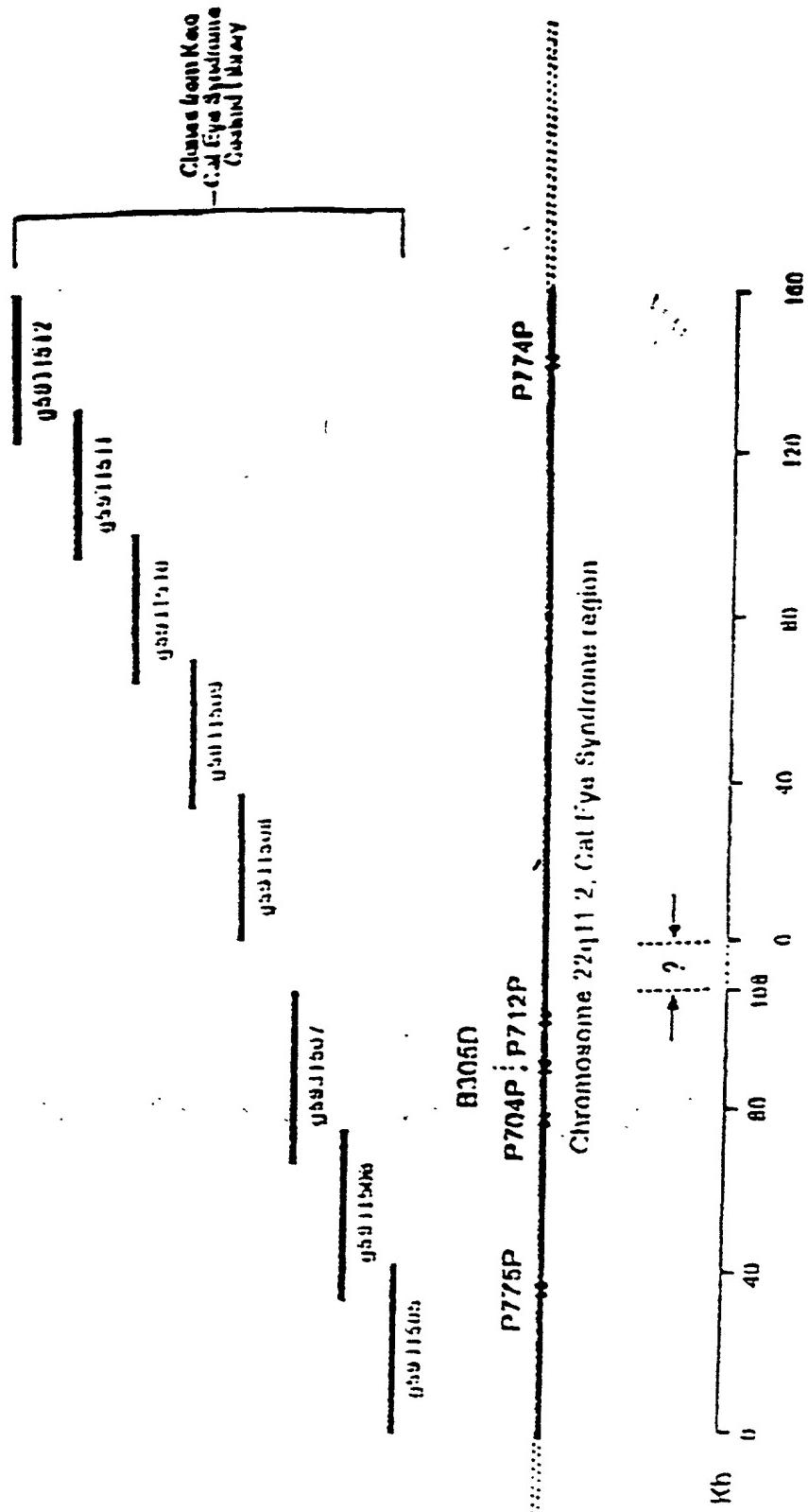
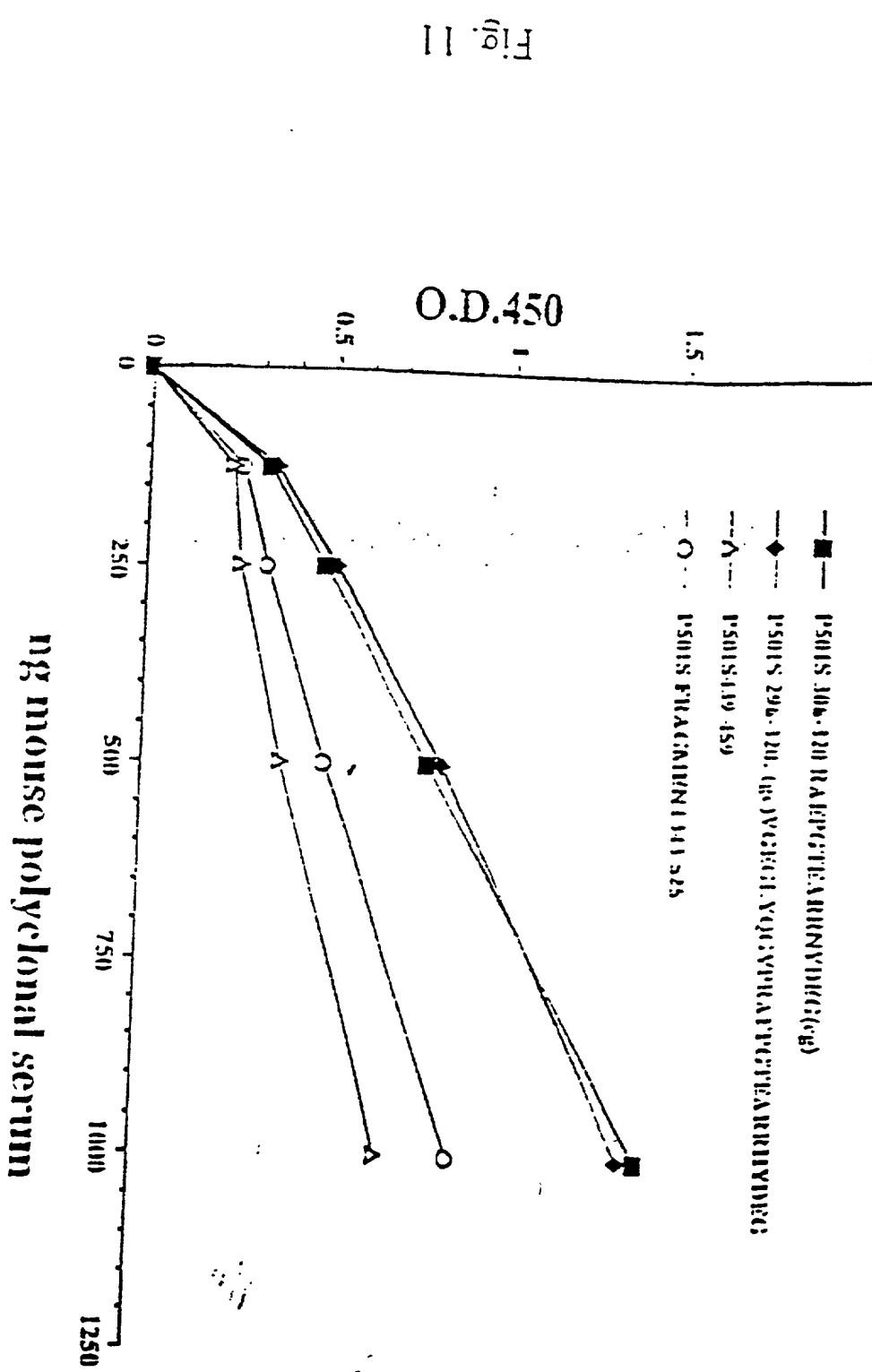


Fig. 10

FIGURE A. ELISA assay of rabbit polyclonal antibody specificity



10 20 30 40 50 60 70
 GTCACTTAGGAAAAGGTGTCTTCGGGCAGCCGGGCTCAGCATGAGGAACAGAACAGAAGGAATGACACTCTGG 70
 ACAGCACCCGGACCCCTGTACTCCAGCGCGTCTCGGAGCACAGACTTGTCTTACACTGAAAGCGACTTGGT 140
 GAATTTATTCAAGCAAATTAAAGAACGAGAATGTGTCTTCTTACCAAAGATTCCAAGGCCACGGAG 210
 AATGTGTGCAAGTGTGGCTATGCCAGAGCCAGCACATGGAAGGCACCCAGATCAACCAAAGTGAGAAAT 280
 GCAACTACAAGAACACACCAAGGAATTCTACCGACGCCCTTGGGATATTAGTTGAGACACTGGG 350
 360 370 380 390 400 410 420
 GAAGAAAGGGAAAGTATATACTGTCTGTCTGCACACGGACCGGAAATCCTTACGAGCTGCTGACCCAG 420
 CACTGGCAGCTGAAAACAACCAACCTGGTCATTTCTGTGACCGGGGGCGCCAAGAACCTCGCCCTGAAGC 490
 CGCGCATGCGCAAGATCTTCAGCGGCTCATCTACATCGCGCAGTCCAAAGGTGCTGGATTCTCACGGG 560
 AGGCACCCATTATGGCCTGACGAAGTACATGGGGAGGTGGTGAGAGATAACACCATCAGCAGGAGTTCA 630
 GAGGAGAAATATTGTGGCCATTGGCATAGCAGCTGGGCATGGTCTGCAACCGGGACACCCCTCATCAGGA 700
 710 720 730 740 750 760 770
 ATTGGGATGGTGGGGCTATTTTAAAGCCCAGTACCTTAATGGATGACTTCACAAGGGATCCACTGTATAT 770
 CCTGGACAAACAAACACACACATTGTGCTGCTGGGACAAATGGCTGTGATGGACATCCCACTGTGCGAAGCA 840
 AAGCTCCGGAATCAGCTAGAGAAAGCATATCTCTGAACGGCACTATTCAAGATTCCAACTATGGTGGCAAGA 910
 TCCCCATTGTGTGTTTGCCAAAGGAGGTGGAAAAGAGACTTTGAAAGGCCATCAATAGCTCCATCAAATA 980
 TAAAAATTGCTTGTTGTTGGTGGTGGAAAGGCTGGGGCGGATGGCTGATGTGATGGCTAGCCTGGTGGAGGTG 1050
 1060 1070 1080 1090 1100 1110 1120
 GAGGATGCCCCGACATCTCTGCCGCAAGGAGAAGCTGGTGGCTTTTACCCCGCACGGTGTGCGG 1120
 TGTCTGAGGGAGGAGACTGAGAGTTGGATCAAATGGCTCAAAGAAATTCTCGAATGTTCTCACCTATTAAAC 1190
 AGTTATTAAATGGAAAGAAAGCTGGGGATGAAATTGTGCAATGCGCATCTCTACGGCTCTATACAAAGCC 1260
 TTCAAGCACCAGTGAGCAAGAACAGGATAACTGGAACTGGCAGCTGAGCTGGAGCTGGAGCTGGAGC 1330
 TGGACTTAGCCAAATGATGAGATTTCACCAATGACCCCGGATGGAGCTGCTGACCTTCAAGAAGTCAT 1400
 1410 1420 1430 1440 1450 1460 1470
 GTTTACGGCTCTCATAAAGGACAGAACCAAGTTGTGGCTCTTCTGGAGAATGGCTTGAACCTACGG 1470
 AAGTTTCTCACCCATGATGCTCTCACTGAACTCTTCTCCAAACCACTTCAGCACGGCTTGTGACCGGAATC 1540
 TGCAAGATCGCCAAGAAATTCTATAATGATGCCCTCTCACTGAGTTGTCTGGAAACTGGTGGCAACCTTCCG 1610
 AAGAGGCTTCCGGAAAGGAAGAACAGAAATGGCCGGGACGAGATGGACATAGAACCTCCACAGACGTGCTCT 1680
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 1760 1770 1780 1790 1800 1810 1820
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Fig. 12A (i)

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Fig. 12A(2)

Fig. 12A(3)

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Fig. 12B

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Jiangchun Xu et al.
Filed : June 13, 2000
For : COMPOSITIONS AND METHODS FOR THERAPY AND
DIAGNOSIS OF PROSTATE CANCER
Docket No. : 210121.42715C15
Date : June 13, 2000

Box Patent Application
Assistant Commissioner for Patents
Washington, D.C. 20231

DECLARATION

Sir:

I, Monica Steinborn, in accordance with 37 C.F.R. § 1.821(f) do hereby declare that, to the best of my knowledge, the content of the paper entitled "Sequence Listing" and the computer readable copy contained within the floppy disk are the same.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated this 13th day of June, 2000.



Monica Steinborn
Legal Assistant

701 Fifth Avenue, Suite 6300
Seattle, WA 98104-7092
(206) 622-4900
FAX (206) 682-6031

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SEQUENCE LISTING

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Mitcham, Jennifer L.
Harlocker, Susan L.
Jiang, Yuqui
Reed, Steven G.
Kalos, Michael D.
Fanger, Gary R.
Retter, Marc W.
Stolk, John A.
Day, Craig H.
Vedvick, Thomas S.
Carter, Darrick
Li, Samuel
Wang, Aijun
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ncccnntng gcnttnann cnaaaaaggc cnnnnacaa tctcctnnnc cctcanttcg	780
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<210> 10
<211> 789
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(789)
<223> n = A,T,C or G

<400> 10

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agatcctgcc ctacacactg gcctccctt accaccggga gaagcaggtg ttccctgccc	180
aataccgagg ggacactgga ggtgctagca gtgaggacag cctgtatgacc agcttcctgc	240
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tgctccacc tccaccccgcg ctctgcgggg cctctgcctg tgatgtctcc gtacgtgtgg	360
tggtggtga gcccaccgan gccagggtgg ttccggcccg gggcatctgc ctggacctcg	420
ccatccttggaa tagtgcctcc tgctgtccca ngtggcccca tccctgttta tgggtccat	480
tgtccagctc agccagtctg tcactgccta tatgggtct gccgcaggcc tgggtctgg	540
cccatttact ttgctacaca ggtantattt gacaagaacg anttggccaa atactcagcg	600
ttaaaaaatt ccagcaacat tgggggttga aggccctgcct cactgggtcc aactccccgc	660
tcctgttaac cccatggggc tgccggctt gcccattt tctgttgc ccaaantnat	720
gtggctctct gctgccaccc tttgctggct gaagtgcnta cngncancnt ngggggtng	780
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<210> 11
<211> 772
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(772)
<223> n = A,T,C or G

<400> 11

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accaacaggg cacatcctga taaaaggtaa gaggggggtg gatcagcaaa aagacagtgc	180

tgtgggctga	ggggacctgg	ttcttgtgt	ttgccccta	ggactctcc	cctacaaata	240
actttcatat	gttcaaattcc	catggaggag	tgttcatcc	tagaaactcc	catgcaagag	300
ctacattaaa	cgaagctgca	ggttaagggg	cttanagatg	gaaaccagg	tgactgagtt	360
tattcagctc	ccaaaaacc	ttctctaggt	gtgtctcaac	taggaggcta	gctgttaacc	420
ctgagcctgg	gtaatccacc	tgcagagtcc	ccgcattcca	gtgcattggaa	cccttctggc	480
ctccctgtat	aagtccagac	tgaaacccccc	ttgaaaggnc	tccagtcagg	cagccctana	540
aactggggaa	aaaagaaaaag	gacgccccan	cccccagctg	tgcanctacg	cacctaaca	600
gcacagggtg	gcagcaaaaa	aaccactta	cttggcaca	aacaaaaact	ngggggggca	660
accccgac	cccnanggg	gttaacagga	ancnggnnaa	cntggAACCC	aatnaggca	720
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<210>	12					
<211>	751					
<212>	DNA					
<213>	Homo sapien					
<220>						
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<223>	n = A,T,C or G					
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agtggcccn	aaaatcttca	aaaaggatgc	cccatcnatt	gacccccc	atgcccactg	600
ccaacagggg	ctgccccacn	cncnnnaacga	tganccnatt	gnacaagatc	tncntggct	660
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<210>	13					
<211>	729					
<212>	DNA					
<213>	Homo sapien					
<220>						
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<222>	(1)...(729)					
<223>	n = A,T,C or G					
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accatgcagt	gtttcagctt	cattaagacc	atgatgatcc	tcttcaattt	gctcatctt	180
ctgtgtggtg	cagccctgtt	ggcagtgggc	atctgggt	caatcgatgg	ggcatccctt	240

ctgaagatct tcgggccact gtcgtccagt gccatgcagt ttgtcaacgt gggctacttc	300
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actgagagca agtgtgcct cgtgacgttc ttcttcattcc tcctcctcat ctgcattgtct	420
gagggtgcaa tgctgtggtc gccttgggtgt acaccacaat ggctgagcac ttccgtacgt	480
tgctggtaat gcctgcccata aaaaaaaat tatgggttcc caggaanact tcactcaagt	540
gttggAACAC cacoatgaaa gggctcaagt gctgtggctt cnncacta tacggatttt	600
gaagantcac ctacttcaaa gaaaanagtg ctttcccccc atttctgttg caattgacaa	660
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attnaaggg	729
<210> 14	
<211> 816	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1)...(816)	
<223> n = A,T,C or G	
<400> 14	
tgctttcct caaagttgtt cttgttgcca taacaaccac cataggtaaa gcggggcgcag	60
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ggcagggtcca cgcagtgcgc tttgtcaactg gggaaatgga tgcgtggag ctgcgtcaaag	180
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tcacactcca gggaaactgtc natgcagcag ccattgctgc agcggaaactg ggtgggctga	300
cangtgcac agcacacactgg atggcgcctt tccatgnnan gggccctgng ggaaagtccc	360
tgancanccan anctgcctct caaangcccc accttgcaca ccccgacagg ctagaatgga	420
atcttcttcc cgaaaggtag ttnttctgt tgcccaancc ancccnntaa acaaactctt	480
gcanatctgc tccgnggggg tcntantacc anctggaa aagaacccca ggcnngcgaac	540
caancttgg tggatncgaa gcnataatct nctnttctgc ttggtgacca gcaccantna	600
ctgtnnanct ttagnccntg gtcctcntgg gttgnncttg aacctaaten cnntcaact	660
gggacaaggta antngccnt ccttnaatt cccnancntn cccctgggtt tgggtttt	720
cncnctccata ccccaagaaan nccgtgtcc ccccaacta gggccnnaaa cnnttnttc	780
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<210> 15	
<211> 783	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1)...(783)	
<223> n = A,T,C or G	
<400> 15	
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aagacccaaa ccaggtggaa ctgtggggac tcaaggaang cacctacctg ttccagctga	180
cagtgactag ctcagaccac ccagaggaca cggccaaacgt cacagtcact gtgtgtcca	240

ccaagcagac agaagactac tgcctcgcat ccaacaangt gggtcgctgc cggggctctt	300
tcccacgctg gtactatgac cccacggagc agatctgcaa gagttcggtt tatggaggct	360
gcttggccaa caagaacaac taccttcggg aagaagagtg cattctancc tgctcnggtg	420
tgcaagggtgg gcctttgana ngcancctcg gggctcangc gactttcccc cagggccccct	480
ccatggaaag gcgcocatcca ntgttctctg gcacctgtca gcccacccag ttccgctgca	540
ncaatggctg ctgoatcnac antttcctng aattgtgaca acaccccccna ntgcccccaa	600
ccctcccaac aaagttccc tggtnaaaaa tacnccant ggcttttnac aaacncccg	660
cncctccntt ttcccnntn aacaaaggc nctngcnntt gaactgcccna aaccnnggaa	720
tctnccnngg aaaaantncc cccccctggtt cctnnaancc cctccnccnaa anctncccc	780
ccc	783
<210> 16	
<211> 801	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1)...(801)	
<223> n = A,T,C or G	
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ttggctgtgt tggtgacggtt gtcattgcaa cagaatgggg gaaaggcact gttcttttg	180
aagttagggtg agtcctcaaa atccgtatag ttggtaagc cacagcactt gagcccttc	240
atggtgtgtt tccacacttg agtgaagtct tcctggaaac cataatcttt cttgatggca	300
ggcactacca gcaacgtcag gaagtgcata gccattgtgg tgtacaccaa ggccgaccaca	360
gcagctgcaaa cctcagcaat gaagatgagg aggaggatga agaagaacgt cncgaggc	420
cacttgctct ccgtttagc accatagcag cccangaaac caagagcaaa gaccacaacg	480
ccngctgca atgaaaagaaa ntacccacgt tgacaaactg catggccact ggacgacagt	540
tggcccgaan atcttcagaa aaggatgcc ccatcgattt aacacccana tgcccactgc	600
cnacagggtgc gcnccnccn gaaagaatga gccattgaag aaggatcncntc ntgtcttaa	660
tgaactgaaa ccntgcatgg tggccctgt tcagggtct tggcagtgaa ttotganaaa	720
aaggaacngc ntnagcccccc ccaaangana aaacacccccc gggtgttgcc ctgaattggc	780
ggccaaggan ccctgccccn g	801
<210> 17	
<211> 740	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1)...(740)	
<223> n = A,T,C or G	
<400> 17	
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cctttgtgga gcctcagcag ttccctctt cagaactcac tgccaagagc cctgaacagg	120
agccaccatg cagtgttca gcttcattaa gaccatgtat atcccttca atttgctcat	180

ctttctgtgt ggtgcagccc tggcatctgg gtgtcaatcg atggggcatc	240
ctttctgaag atcttcgggc cactgtcgac cagtccatg cagtttgtca acgtgggcta	300
cttcctcatc gcagccggcg ttgtggtctt tgctcttgggt tcctggct gctatggtc	360
taagacggag agcaagtgtg ccctcggtac gtttttttccatc atccctctcc tcatcttcat	420
tgctgaagtt gcagctgtg tggtcgcctt ggtgtacacc acaatggctg aaccattcct	480
gacgttgcgtg gtantgcctg ccatcaanaa agattatggg ttcccaggaa aaattcactc	540
aantntggaa cacnccatg aaaaggcgtc caatttctgn tggcttcccc aactataccg	600
gaattttgaa agantcnccc tacttccaaa aaaaaanant tgccttncc cccnttctgt	660
tgcaatgaaa acntcccaan acngccaatn aaaacctgcc cnnncaaaaaa ggntcncaa	720
aaaaaaaaant nnaagggttn	740

<210> 18
 <211> 802
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(802)
 <223> n = A,T,C or G

<400> 18

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ggatacacct tacttagca gccagggtga caactgagag gtgtcgaagc ttattcttct	180
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aagcaaacac tgtgagcagc cggaaaggtag aggcaagtc actctcagcc agctctctaa	300
cattggccat gtccagcagt tctccaaaca cgtagacacc agnggcctcc agcacctgat	360
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ggttctgccc tgtcacccatc acttccgcac tcatcactgc actgagtggtg ggggacttgg	480
gctcaggatg tccagagacg tggttccgccc ccctcnctta atgacaccgn ccanncaacc	540
gtcggctccc gccgantngn ttctgtcgtnc ctgggtcagg gtctgctggc cnctacttgc	600
aancttcgtc nggcccatgg aattcaccc accggaactn gtangatcca ctnnttcttat	660
aaccggncgc caccgcnnt ggaactccac tttttttncc tttacttgag ggttaaggtc	720
acccttnncg ttaccttggt ccaaaccntn ccntgtgtcg anatngtnaa tcnggnccna	780
tnccancncncc atangaagcc ng	802

<210> 19
 <211> 731
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(731)
 <223> n = A,T,C or G

<400> 19

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cntgaccncc actccccncc ncncantgca gtatgagtg cagaactgaa ggttacgtgg	180

caggaaccaa gancaaannc tgctccnnntc caagtccgcn naggggcg ggctggccac	240
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catgcccagn gttanataac nggcngagag tnannttgcc tctcccttcc ggctgcgcan	360
cgngtntgct tagnggacat aacctgacta cttaactgaa cccnngaatc tnccnccct	420
ccactaagct cagaacaaaa aacctcgaca ccactcantt gtcacctgnc tgctcaagta	480
aagtgtaccc catncccaat gtntgctnga ngctctgncc tgcnntangt tcggtcctgg	540
gaagacctat caattnaagc tatgtttctg actgccttctt gctccctgna acaancnacc	600
cnnccnntcca agggggggnc ggcccccaat cccccaacc ntnaattnan tttancccn	660
cccccnngcc cggccttta cnancntnn nnacngggna aaaccnnngc ttncccaac	720
nnaatccncc t	731

<210> 20
<211> 754
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(754)
<223> n = A,T,C or G

<400> 20	
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annttaaatt aaattnnnt tggnggnna anccnaatgt nangaaagtt naacccanta	180
tnancttnaa tncctggaaa ccngtngntt ccaaaaatnt ttaaccctta antccctccg	240
aaatngttta ngaaaaccc aanttctcnt aaggttgttt gaaggntnaa tnaaaanccc	300
nnccaattgt tttngccac gcctgaatta attggnttcc gntgtttcc nttaaaaanaa	360
ggnnancccc ggttantnaa tccccccnncc cccaaattata ccgantttt ttngaattgg	420
ganccncgg gaattaacgg ggnnnntccc tnttgggggg cnggnncccc cccntcggg	480
ggttngggnc aggncnnaat tggtaaggg tccaaaaat ccctccnaga aaaaaanctc	540
ccaggnntgag nntngggttt nccccccccc cangggccct ctcgnanagt tgggtttgg	600
ggggcctggg atttnttcc ccctnttncc tccccccccc ccnggganag aggtngngt	660
tttgntcncc ggcnnccnn aagancttn ccganttnan ttaaatccnt gcctnggcga	720
agtccnttgn agggntaaan ggccccctnn cggg	754

<210> 21
<211> 755
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(755)
<223> n = A,T,C or G

<400> 21	
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nncanatncc actganngcg cgangtngan ngagaaanct nataccanag ncacccanacn	180
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nncnnccanat gatttcctn anccgattac ccntncccc tancccctcc cccccaacna	300
cgaaggcnct ggnccnaagg nngcgncnc cgcgtagntc cccnncaagt cnncncnccta	360
aactcanccn nattacncgc ttcntgagta tcactccccg aatctcaccc tactcaactc	420
aaaaanatcn gatacaaataatncaagcc tgnttatnac actntgactg ggtctctatt	480
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gggctcntct tttccttcgg ttancctggn ttcnncggc cagttattat ttcccntttt	660
aaattcnnc cnttanta tggcnnctcna aaccccccggc cttgaaaacg gccccctggt	720
aaaaggttgtt ttganaaaaa tttttgtttt gtcc	755
<210> 22	
<211> 849	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1)...(849)	
<223> n = A,T,C or G	
<400> 22	
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cataactcng nggcctgccc caccacccg ggcggccng ngnccggcc cgggtcattn	240
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cngccntcta nccnncngcc cccctccant nngggggact gccnanngct ccgttnctng	420
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nncangcgg	849
<210> 23	
<211> 872	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1)...(872)	
<223> n = A,T,C or G	
<400> 23	
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cacacncnan aganaaatcc nctgccttcc anagtnacn attgaacnng agaaccangc	180

nggcgaatcg	taatnaggcg	tgcgcccca	atntgtcncc	gtttatttnn	ccagcntcnc	240
ctnccnaccc	tacntcttcn	nagctgtcn	accctngtn	cgnacccccc	naggtcgaaa	300
tcgggttnn	nntgaccgng	cnnccctcc	ccccntccat	nacgancnc	ccgcaccacc	360
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accgcattga	ccctcgccnn	ctncnngaaa	ncgnanacgt	ccggggttgnn	annancgctg	480
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ccncgcccnc	tcnnncacnc	cctgggacgc	tntcctntgc	cccccttnac	tccccccctt	600
cgncgtgncc	cgncccccacc	ntcatttnca	nacnttcc	acaannncct	ggntnnctcc	660
cnancngncn	gtcanccnag	ggaagggngg	ggnccnnntg	nttacgttg	ngngangtc	720
cgaanantcc	tcnccntcan	cnctaccct	cggcgnct	ctcngttncc	aacttancaa	780
ntctccccc	ngngcncntc	tcagcctcnc	ccncccnct	ctctgcantg	tnctctgctc	840
tnaccnntac	gantntcgn	cnccctcttt	cc			872
<210>	24					
<211>	815					
<212>	DNA					
<213>	Homo sapien					
<220>						
<221>	misc_feature					
<222>	(1)...(815)					
<223>	n = A,T,C or G					
<400>	24					
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tcntncattt	gtaacaantg	tnntgtccat	cctgtcngan	canattccca	tnnattncgn	180
cgcattcncc	gcncantatn	taatngggaa	ntcnntnnnn	ncacccnccat	ctatcntncc	240
gcncctgtac	tggnagagat	ggatnantic	tnntntgacc	nacatgttca	tcttggattn	300
aananccccc	cgcngnccac	cggttngnng	cnagccnntc	ccaagacctc	ctgtggaggt	360
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gatcccggtcc	aggnttnacc	atcccttcnc	agcgcctt	ttngtgcctt	anagngnagc	480
gtgtccnanc	cnctcaacat	ganacgcgcc	agnccanccg	caattnggca	caatgtcgnc	540
gaacccctta	ggggantna	tncaaanc	caggattgtc	cncncangaa	atcccncanc	600
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ccccacccgt	nncntgaaa	gggtgaanct	cngnntcanc	cngncgaggn	ntcngaagga	720
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tcttacggaa	gggcctgggc	cncttncaa	ggttggggga	accnaaaaatt	tcnctntgc	660
ccncccncca	cnntcttngng	nnncncanitt	ggaacccttc	cnattccctt	tggcctcnna	720
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<210>	26					
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<212>	DNA					
<213>	Homo sapien					
<220>						
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<222>	(1)...(820)					
<223>	n = A,T,C or G					
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cccanagata	ncttatanca	acagtgcctt	gaccaagagc	tgctgggcac	atttcctgca	120
aaaaaggtgg	cgggtccccat	cactcctcct	ctcccatagc	catcccagag	gggtgagtag	180
ccatcangcc	ttcgggtggga	gggagtcang	gaaacaacan	accacagagc	anacagacca	240
ntgatgacca	tggcgggag	cgagccttct	ccctgnaccg	gggtggcana	nganagccta	300
nctgagggggt	cacaactataa	acgtaaacga	ccnagatnan	cacctgcttc	aagtgcaccc	360
ttcctacctg	acnaccagng	accnnnaact	gcnccctggg	gacagcnctg	ggancagcta	420
acnnagca	cacctgcccc	cccatggccg	tngcntccc	tggtcctgnc	aagggaaagct	480
ccctgttgg	attnccggga	naccaaggga	ncccccctct	ccanctgtga	agaaaaaann	540
gatggaaattt	tncccttcgg	gcnntcccc	tccctttta	cacgccccct	nntactcntc	600
tccctctntt	ntccctgnnc	acttttnacc	ccnnnatttc	ccttnattga	tcggannctn	660
ganattccac	tnncgcctnc	cncnatcng	naanacnaaa	nactntctna	cccnngggat	720
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<210>	27					
<211>	818					
<212>	DNA					
<213>	Homo sapien					
<220>						
<221>	misc_feature					
<222>	(1)...(818)					
<223>	n = A,T,C or G					
<400>	27					
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ctgctgagca ctcccgcccc tcaccctgcc cagccctgc catgagctct gggctggtc	240
tccgcctcca gggttctgt cttccangca nccancaag tggcgctggg ccacactggc	300
ttcttcctgc cccntccctg gctctgantc tctgtcttcc tgcctgtgc angncncttg	360
gatctcagt tccctcnctc anngaactct gttctgann tcttcantta actntgantt	420
tatnaccnan tggncgtnc tgtnactt taatggccn gaccggctaa tccctccctc	480
nctcccttcc anttcnnna accngctnc cntcntctcc ccntanccg ccngggaaanc	540
ctccttgcc ctnaccangg gcnnnacccg ccntnnctn gggggcnng gtnctncnc	600
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tnnctcttcn ngtntcgnaa ngntcnctn tnnnnngncn ngntnnntncn tccctctcnc	720
cnnntgnang tnnttnnnnc ncngnncccc nnncnnnnnn nggnnntnnn tctncncngc	780
ccnnccccc ngnattaagg cctccnnctc ccggccnc	818
<210> 28	
<211> 731	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
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<223> n = A,T,C or G	
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gattnaaccc cattgtatgg agnnaaaggn tttnagggat tttcggctc ttatcagtat	180
ntanattcct gtnaatcgga aaatnatntt tcnnncngaa aatnttgctc ccatccgnaa	240
attnctcccg ggttagtgcatt ntnggggn cngccangtt tcccaggctg ctanaatcgt	300
actaaagnnt naagtgggan tncaaataa aacccnncac agagnatccn taccgcactg	360
tnnnttnct tcgcctntg actctgcnnn agccaaatac ccnnngngnat gtcnccngn	420
nnngcncnc taaaannnc tcngngctnn gancatcang gggtttcgca taaaaagcnn	480
cgttncat naaggcactt tngcctcatc caaccnctng ccctcnccca ttngccgtc	540
ngttcnct acgctnnntng cncctnnntn ganatttnc ccgcctnggg naancctcct	600
gnaatgggta gggncntntc ttttnaccnn gnggtntact aatcnctnc acgnctnctt	660
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nnnccannnc c	731
<210> 29	
<211> 822	
<212> DNA	
<213> Homo sapien	
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<221> misc_feature	
<222> (1)...(822)	
<223> n = A,T,C or G	
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cgctcanacc tcacancctc ccnacnangc ctataangaa nannaataga nctgtncnnt	120
atntntacnc tcatannctc cnnnaccac tcctcttaa cccntactgt gcctatngcn	180
tnnctantct ntgcgcctn cnanccacn gtggccnac cncnngnatt ctcnatctcc	240
tcnccatntr gcctananta ngtnccatacc ctatacctac nccaatgcta nnctaannc	300
tccatnatt annntaacta ccactgacnt ngacttgcnc atnanctcct aatttgaatc	360
tactctgact cccacngcct annnattagc ancncatcccc nacnatntct caaccaaato	420
ntcaacaacc tatctanctg ttcncccaacc nttnccctcg atccccnnac aacccccctc	480
ccaaatacc nccacctgac ncctaaccn caccatcccc gcaagccnan ggncatttan	540
ccactggaat cacnatngga naaaaaaaaaac ccnaactctc tanncnnat ctccctaana	600
aatnctctn naatttactn ncantncat caancccacn tgaaacnnaa cccctgtttt	660
tanatccctt cttdcgaaaa ccnaccctt annncccaac ctttngggcc ccccnctnc	720
ccnaatgaag gncncccaat cnangaaacg nccntgaaaa ancnaaggcna anannntccg	780
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<210> 30
 <211> 787
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(787)
 <223> n = A,T,C or G

<400> 30

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ctagagaaga ctttctctcc tactgtcatt atggagccct gcagactgag ggctccctt	120
gtctgcagga tttgtatgtct gaagtcgtgg agtgtggctt ggagctcctc atctacatna	180
gtctggaaagcc ctggaggggcc tctctcgcca gcctccccc tctctccacg ctctccangg	240
acaccagggg ctccaggcag cccattattc ccagnangac atgggtttc tccacgcgga	300
cccatggggc ctgnaaggcc agggtctctt ttgacaccat ctctcccgct ctgcctggca	360
ggccgtggga tccactantt ctanaacggn cgccaccnccg gtgggagctc cagctttgt	420
tcccnttaat gaaggttaat tgcncgcttgcgtaatcat nggtcanaac tnttcctgt	480
gtgaaattgt ttntccctc ncattccnc ncacatacn aacccggaaan cataaagtgt	540
taaaggcctgg gggtnccctn nngaatnaac tnaactcaat taattgcgtt ggctcatggc	600
ccgccttccn ttcnngaaaa ctgtcntccc ctgcntnnnt gaatcggcca ccccccnggg	660
aaaagcggtt tgcnttttng ggggntcctt ccnctcccc cctcnctaann cctcnccct	720
cggtcgttnc nggtngcggg gaangggnat nnctccnc naagggggng agnnngntat	780
ccccaaaa	787

<210> 31
 <211> 799
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(799)
 <223> n = A,T,C or G

<400> 31

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aacaaaggac tcctgcagcc ttctctgtct gtctcttggc gcagggcacat ggggaggcct	180
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ggggaccttc tgttctccca ngnnaacttc ntnnatctn aaagaacaca actgtttctt	360
cngcanttct ggctgttcat ggaaagcaca ggttccnat ttnggctggg acttggtaca	420
tatggttccg gcccacctct cccntcnaan aagtaattca ccccccccn ccntctntt	480
cctgggcct taantaccca caccggaact canttantta ttcatcttng gntgggcttg	540
ntnatcncn cctgaangcg ccaagttgaa agggcacgccc gtncncnctc cccatagnan	600
nttttncnt canctaattgc ccccccnggc aacnatccaa tcccccccn tgggggcccc	660
agcccanggc ccccgncnctg ggnnnccnngn cncgnantcc ccaggnctc ccantcngnc	720
ccnnngcncc cccgcacgca gaacanaagg ntngagccnc cgcannnnn nggtnncnac	780
ctcgcccccc cnncgnng	799

<210> 32
 <211> 789
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(789)
 <223> n = A,T,C or G

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ggcaacaggc tccggcggcg gccggcggcg ccctacctgc ggtaccaaatt ntgcagccctc	180
cgctcccgct tgatttcct ctgcagctgc aggatgccnt aaaacaggc ctcggccntn	240
ggtgggcacc ctgggattn aatttccacg ggcacaatgc ggtcgcancc cctcaccacc	300
nattaggaat agtggtnna cccnccnccg ttggcnact ccccntggaa accactntc	360
gcggctccgg catctggct taaaccttgc aaacnctggg gcccttntt tggttantnt	420
nccngccaca atcatnactc agactggcnc gggctggccc caaaaaanncn ccccaaaacc	480
ggncatgtc ttnncgggt tgctgcnatn tncatcacct cccgggnca ncaggncaac	540
ccaaaaagttc ttgnngccn caaaaaanct cgggggggncc ccagttcaa caaagtcatc	600
ccccctggcc cccaaatcct ccccccgnnt nctgggtttg ggaaccacg cctctnnctt	660
tggnngccaa gntggntccc ccttcggcnc cccgggtggc ccnnctctaa ngaaaacncc	720
ntcctnnnca ccatcccccc nnngnnacgnc tancaangna tcccttttt tanaaacggg	780
ccccccnccg	789

<210> 33
 <211> 793
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(793)
 <223> n = A,T,C or G

<400> 33

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gactaaagtgc tgatgaactt	cccaatcaga tgacatgga tgattggcca gaaatgaana	180
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acaangaacg gggctcg	ttt atcaccantg aggagcagga cgtgagcccc cgccctgcac	360
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ggncgccacc	gccccggggc tccagcttt gttccctta gtgagggtta attgcgcgt	480
tggcgtaatc atggtcata	ctgtttcctg tggaaattt ttatccgctc acaattccac	540
acaacatacg anccggaagc	atnaaatttt aaagcctggn ggtngctaa tgantgaact	600
nactcacatt aattggctt	gctcaactg cccgcttcc agtccggaaa acctgtccctt	660
gccagctgcc nttaatgaat	cngccaccc cccggggaaa aggcngettgc ttnttgggg	720
cgcncttccc gcttctcg	c ttcctgaant cttcccccc ggtcttcgg cttgcggcna	780
acggtatcna cct		793

<210> 34

<211> 756

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(756)

<223> n = A,T,C or G

<400> 34

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ancaagtgcg gggaaanagct	gggtcgactc aagctagttc ttctggagct caacttcttgc	120
ccaaaccacag ggaccaagct	gaccaaacag cagctaattc tggccctgtga catactggag	180
atcggggccc aatggagcat	cctacgcaan gacatcccct cttcgagcg ctacatggcc	240
cagctcaa at gctactactt	tgattacaan gagcagctcc ccgagtcagc ctatatgcac	300
cagctttgg gcctcaacct	cctttcctg ctgtcccaga accgggtggc tgantnccac	360
acggantttg ancggctgcc	tgcccaanga catacanacc aatgtctaca tcnaccacca	420
gtgtccttgg gcaatactga	tgganggcag ctaccncaaa gtnttcctgg ccnaggtaa	480
catccccccgc cgagagctac	accttcttca ttgacatcct gctcgacact atcagggatg	540
aaaatcgcn	ggttgcctca gaaaggctnc aanaanatcc tttcnctga aggcccccg	600
atncnctagt nctagaatcg	gccccccatc gcgtgganc ctccaacctt tcgttnccct	660
ttactgaggg ttnattgccg	cccttggcgt tatcatggc acnccngttn cctgtgttga	720
aattnttaac cccccacaat	tccacgcna catng	756

<210> 35

<211> 834

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(834)

<223> n = A,T,C or G

<400> 35

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tagtcagaca cnctcttggg caaaaaaacan cagatntga gtcttgattt cacctccaat	180
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aaantccanc angtctcct tggtgacctc cccttcaaag ttgttccggc cttcatcaa	300
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ggaaaactgat cccaaatggt atgtcatcca tcgcctctgc tgccctgaaa aaacttgctt	420
ggcncaaatac cgactccccn tccttgaag aagccnatca cacccttcc cctggactcc	480
nncaangact ctncgcgtnc cccntccnng cagggttgg ggcannccgg gcccngcgc	540
ttcttcagcc agttcacnat nttcatcagc ccctctgcca gctgttnat tccttgggg	600
ggaancgc tcctccctcc tgaannaact ttgaccgtng gaatagccgc gcntcnccnt	660
acntnctggg ccgggttcaa antccctccn ttgnncnntcn cctcgggcca ttctggattt	720
nccnaacttt ttccctcccc cnccccncgg ngtttggntt ttcatnnggg ccccaactct	780
gctnttggcc antccccctgg gggcntntan cnccccctnt ggtcccntrng ggcc	834

<210> 36

<211> 814

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(814)

<223> n = A,T,C or G

<400> 36

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cctagnaaac attaatgggt tgctctacta atacatcata cnaaccagta agcctgccc	120
naacgcac ac tcaggccatt cctaccaaag gaagaaaggc tggctctcc acccccgt	180
ggaaaaggc gccttgcgtt acaccacaat ncggctgaat cttaagtctt gtgtttact	240
aatggaaaaa aaaaataaaac aanaggttt gttctcatgg ctgcccaccc cagcctggca	300
ctaaaacanc ccagcgctca cttctgcctt ganaaatatt ctttgctctt ttggacatca	360
ggcttgcgtt tatcaactgac acnnttcac ccagctggc ncccttcccc catntttgtc	420
antganctgg aaggcctgaa ncttagtctc caaaagtctc ngcccacaag accggccacc	480
aggggangtc nttnccatgt gatctgcac anantaccn tatcatcnnt gaataaaaag	540
gcccctgaac ganatgcttc cancancctt taagacccat aatcctngaa ccatgggtgc	600
cttccggct gatccnaaag gaatgttctt gggcccant ccctccttgc ttncttacgt	660
tgtnttggac ccntgctngn atnacccan tganatcccc ngaagcaccc tncccctggc	720
atttgantt cntaaattct ctgccttacn nctgaaagca cnattccctn ggcnccnaan	780
ggngaaactca agaaggctn ngaaaaacca cncn	814

<210> 37

<211> 760

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(760)

<223> n = A,T,C or G

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<212> DNA	
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tcgaa	305
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<211> 852	
<212> DNA	
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<212> DNA
<213> Homo sapien

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<210> 46
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<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
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<223> n = A,T,C or G

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aagaagataa tatattccaa gcanatacaa aatatctaatt gaaagatcaa ggcaggaaaa     180
tgantataac taattgacaa tggaaaatca attttatgt gaattgcaca ttatccttta     240
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ttacaatggc ttaaatgcan ggaaaaagca gtgaaagtag ggaagtantic aaggtcttc    420
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ggctctgtt atatccacaa tcccagcagc aagatgaagg gatgaaaaag gacacatgct    540
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<210> 47
<211> 774
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(774)
<223> n = A,T,C or G

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cctcatccct ggaggacgac agtggaggaa caactgacca tgtccccagg ctctgtgtg    360
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aggctgctgg cttcaaattn tggctcattt acgagctatg ggaccttggg caagtnatct	720
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<222> (1) ... (124)	
<223> n = A,T,C or G	
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<211> 147	
<212> DNA	
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<222> (1) ... (147)	
<223> n = A,T,C or G	
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tttagggcacc catatcccaa gcantgt	147
<210> 50	
<211> 107	
<212> DNA	
<213> Homo sapien	
<400> 50	
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<210> 51	
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<400> 51	60
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<222> (1)...(484)	
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aatgattggc aggtcnggta aatnccaaaa catattccaa ctcaacactt ttTTCCNCG	420
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tctatgtcct ctcaagtgcc ttttgtttt t      151

    <210> 55
    <211> 91
    <212> DNA
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gcctccagt ggatactcga gccaaagtgg t      91

    <210> 56
    <211> 133
    <212> DNA
    <213> Homo sapien

    <400> 56
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    <210> 57
    <211> 147
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    <220>
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    <223> n = A,T,C or G

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    <220>
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    <223> n = A,T,C or G

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aaacatggan agattggtgc tgganatcgc cgtggctatt cctcattgtt attacanagt	240
gaggttctct gtgtgccccac tggttgaaa accgttctnc aataatgata gaatagtaca	300
cacatgagaa ctgaaaatggc ccaaaccag aaagaaagcc caactagatc ctcagaanac	360
gcttcttaggg acaataaccg atgaagaaaa gatggcctcc ttgtgcccccc gtctgttatg	420
atttctctcc attgcagcnnaaaacccgtt cttctaagca aacncagggtg atgatggcna	480
aaatacaccc cctcttgaag naccngggagg a	511
<210> 73	
<211> 499	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	

<222> (1)...(499)	
<223> n = A,T,C or G	
<400> 73	
cagtgccagc actggtgcca gtaccagtac caataacagt gccagtgcca gtgccagcac	60
cagtggcgc ttcagtgcgt gtgccagct gaccgcact ctcacattt ggctcttcgc	120
tggccttgtt ggagctggc ccagcaccag tggcagctct ggtgcctgtg gtttctccct	180
caagttagat tttagatattt gttaatctcg ccagtcttc tcttcaagcc agggtgcatc	240
ctcagaaacc tactcaaacac agcactctag gcagccacta tcaatcaatt gaagttgaca	300
ctctgcattt aatctattt ccatttctga aaaaaaaaaaaa aaaaaaaaggg cgccgcctcg	360
antcttagagg gcccgtttaa acccgctgat cagcctcgac tgtgccttct anttgcagc	420
catctgttgtt ttgccccctcc cccgntgct tccttgaccc tggaaagtgc cactcccact	480
gtcctttcctt aantaaaat	499
<210> 74	
<211> 537	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1)...(537)	
<223> n = A,T,C or G	
<400> 74	
tttcatagga gaacacactg aggagatact tgaagaattt ggattcagcc gcaagagat	60
ttatcagtt aactcagata aaatcatgtt aagtaataag gtaaaagcta gtctctaact	120
tccaggccca cggctcaagt gaatttgaat actgcattt cagtgttagag taacacataa	180
cattgtatgc atggaaacat ggaggaacag tattacagtgt tcctaccact ctaatcaaga	240
aaagaattac agactctgtat tctacagtgt tgattgaatt ctaaaaatgg taatcattag	300
ggctttgtat ttataanact ttgggtactt atactaaattt atggtagtta tactgccttc	360
cagtttgctt gatatattt ttgatattaa gattcttgac ttatattttt aatgggttct	420
actgaaaaan gaatgtatata ttcttgaaga catcgatata catttatattt cactcttgat	480
tctacaatgtt agaaaatgaa gaaaaatggcc caaattgtat ggtgataaaaa gtcgggt	537
<210> 75	
<211> 467	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1)...(467)	
<223> n = A,T,C or G	
<400> 75	
caaanaacat tgttcaaaag atgcaaattttt tacactactg ctgcagctca caaacaccc	60
tgcattttttt acgtacccctt ccctgctcctt caagtagtgtt ggtctattttt gccatcatca	120
cctgctgtct gcttagaaga acggcttctt gctgcanggg agagaaaatca taacagacgg	180
tggcacaagg agggccatctt ttccatcg gttattgtcc cttagaagcgt ctcttgagga	240
tctagttggg ctttttttt ggggttgggc catttcattt ctcatgtgt tactattctt	300

tcattattgt ataacggttt tcaaaccngt gggcacncag agaacacctac tctgtataaa	360
caatgaggaa tagccacggt gatctccagc accaaatctc tccatgtnt tccagagctc	420
ctccagccaa cccaaatagc cgctgctatn gtgtagaaca tccctgn	467
<210> 76	
<211> 400	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1) ... (400)	
<223> n = A,T,C or G	
<400> 76	
aagctgacag catcgccgc gagatgtctc gctccgtggc cttagctgtg ctgcgcgtac	60
tctctcttgc tggcctggag gctatccagc gtactccaaa gattcagggt tactcacgtc	120
atccagcaga gaatggaaag tcaaattcc tgaattgcta tgtgtctggg tttcatccat	180
ccgacattga agttgactta ctgaagaatg gagagagaat tgaaaaagtg gagcattcag	240
acttgtcttt cagcaaggac tggtcttct atctcttgta ctacactgaa ttcccccca	300
ctgaaaaaga tgagtatgcc tgccgtgtga accatgtgac tttgtcacag cccaagatng	360
ttnagtgaaa tcganacatg taagcagcan catgggaggt	400
<210> 77	
<211> 248	
<212> DNA	
<213> Homo sapien	
<400> 77	
ctggagtgcc ttgggtttc aagccctgc aggaagcaga atgcacccccc tgaggcacct	60
ccagctgccc cggcggggga tgcgaggctc ggagcacccct tgcccggtg tgattgctgc	120
cagggactgt tcatctcagc ttttctgtcc ctttgctccc ggcaagcgct tctgctgaaa	180
gttcatatatct ggagcctgat gtcttaacga ataaaggccc catgctccac ccgaaaaaaaaa	240
aaaaaaaaaa	248
<210> 78	
<211> 201	
<212> DNA	
<213> Homo sapien	
<400> 78	
actagtccag tgggtggaa ttccattgtg ttggcccaa cacaatggct accttaaca	60
tcacccagac cccgcccgc cctgtccccc cgctgctgt aacgacagta tgatgcttac	120
tctgctactc ggaaactatt ttatgtaat taatgtatgc tttttgttt ataaatgcct	180
gatttaaaaa aaaaaaaaaa a	201
<210> 79	
<211> 552	
<212> DNA	
<213> Homo sapien	

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<220>
<221> misc_feature
<222> (1)...(552)
<223> n = A,T,C or G

<400> 79
tcctttgtt aggttttga gacaacccta gacctaaact gtgtcacaga cttctgaatg      60
tttaggcagt gctagtaatt tcctcgtaat gattctgtt ttactttcct attctttatt      120
cctctttctt ctgaagatta atgaagtga aaattgaggt ggataaatac aaaaaggtag      180
tgtgatagta taagtatcta agtgcagatg aaagtgtgtt atatatatcc attcaaaatt      240
atgcaaggta gtaattactc agggtaact aaattactt aatatgctgt tgaacctact      300
ctgttccttg gctagaaaaaa attataaaca ggactttgtt agtttggaa gccaaattga      360
taatattctt tgttctaaaaa gttgggctat acataaanta tnaagaaata tggaattttt      420
ttcccaggaa tatggggttc atttatgaat antacccggg anagaagttt tgantnaaac      480
cngtttttgtt taatacgtt atatgtcctn aatnaacaag gcntgactta tttccaaaaaa      540
aaaaaaaaaa aa      552

<210> 80
<211> 476
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(476)
<223> n = A,T,C or G

<400> 80
acagggattt gagatgctaa ggccccagag atcggttcat ccaaccctct tattttcaga      60
ggggaaaatg gggcttagaa gttacagagc atctagctgg tgcgctggca cccctggcct      120
cacacagact cccgagtagc tgggactaca ggcacacagt cactgaagca gcccctgttt      180
gcaattcactt ttgccacactc caacttaaac attcttcata tgtgatgtcc ttatgtacta      240
aggttaaact ttcccaccca gaaaaggcaa cttagataaa atcttagagt actttcatac      300
tcttctaagt cctttccag ctcactttt agtccttcctt ggggggtgat aggaantntc      360
tcttggctt ctcaataaaaaa tctctatcca tctcatgttt aatttggtagt gcntaaaaat      420
gctgaaaaaa ttaaaaatgtt ctggtttcnc ttaaaaaaaaa aaaaaaaaaa aaaaaaa      476

<210> 81
<211> 232
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(232)
<223> n = A,T,C or G

<400> 81
tttttttttg tatgcncnctn ctgtggngtt attgttgctg ccaccctgga ggagcccaagt      60
ttcttctgtt tcttttttctt ctgggggatc ttctggctc tgccccctcca ttcccagcct      120
ctcatccccca tcttgcactt ttgcttagggt tggaggcgct ttctgttag cccctcagag      180

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actcagtcag cgggaataag tcctagggtt ggggggtgtg gcaagccgc ct 232
 <210> 82
 <211> 383
 <212> DNA
 <213> Homo sapien

 <220>
 <221> misc_feature
 <222> (1)...(383)
 <223> n = A,T,C or G

 <400> 82

 aggcgggagc agaagctaaa gccaaagccc aagaagagtgcagtgccactgggtgcc
 agtaccagta ccaataacat gccagtgcac gtgcgcac cagtggtggc ttcagtgcgt
 gtgccgcct gaccgcact ctcacatttgcgttgcgc tggccttggt ggagctgggt
 ccagcaccag tggcagctct ggtgcctgtg gtttctccta caagtggat tttagatatt
 gttaatcctg ccagttttc tcttcaagcc aggggtgcata ctcagaaacc tactcaacac
 agcactctng gcagccacta tcaatcaatt gaagttgaca ctctgcatta aatctatatttgc
 ccatttcaaaa aaaaaaaaaaaa aaa 383

 <210> 83
 <211> 494
 <212> DNA
 <213> Homo sapien

 <220>
 <221> misc_feature
 <222> (1)...(494)
 <223> n = A,T,C or G

 <400> 83

 accgaattgg gaccgctggc ttataagcga tcatgtcctc cagtattacc tcaacgagca
 gggagatcga gtctatacgc tgaagaaatt tgacccgatg ggacaacaga cctgctcagc
 cccatcctgct cggttctccc cagatgacaa atactctcga caccgaatca ccatcaagaa
 acgcttcaag gtgtcatga cccagcaacc gcgcctgtc ctctgagggt cttaaactg
 atgtcttttc tgccacctgt taccctcggttgcgttgcata accaaactct tcggactgtg
 agccctgatg ccttttgcc agccataactc tttggcntcc agtctctgttgcgttgcata
 tatgcttgcgttgcgttgcata atgggtggcat caccctnnaa gggAACACAT ttgantttt
 tttcncatat tttaaattac naccagaata ntccagaata aatgaattga aaaaactctta
 aaaaaaaaaaaa aaaa 494

 <210> 84
 <211> 380
 <212> DNA
 <213> Homo sapien

 <220>
 <221> misc_feature
 <222> (1)...(380)
 <223> n = A,T,C or G

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<400> 84
gctggtagcc tatggcgtgg ccacggangg gtcctgagg cacggacag tgacttcca      60
agtatcctgc gccgcgtctt ctaccgtccc tacctgcaga tcttcggca gattccccag     120
gaggacatgg acgtggccct catggagcac agcaactgct cgtcggagcc cggcttctgg     180
gcacaccctc ctggggccca ggccggcacc tgctctccc agtatccaa ctggctggtg     240
gtgctgctcc tcgtcatctt cctgctcgta gccaacatcc tgctggcac ttgctcattg     300
ccatgtttag ttacacattc ggcaaagtac aggcaacag cnatctcac tggttggaggcc     360
agcgtnccg cctcatccgg                                         380

<210> 85
<211> 481
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(481)
<223> n = A,T,C or G

<400> 85
gagttagtc ctccacaacc ttgatgaggt cgtctgcagt ggccctctgc ttcataccgc      60
tnccatcgta atactgttagg tttgccacca cctcctgcac cttggggcgg ctaatatcca     120
ggaaactctc aatcaagtca ccgtcnatna aacctgtggc tggttctgtc ttccgctcg     180
tgtgaaagga tctccagaag gagtgcgtga tcttcccac actttttagt acttttattga     240
gtcgattctg catgtccagc aggaggtgtt accagcttc tgacagttag gtcaccagcc     300
ctatcatgcc nttgaacgtg ccgaagaaca ccgagccttg tgtgggggt gnagtctcac     360
ccagattctg cattaccaga nagccgtggc aaaaganatt gacaactcgc ccaggnngaa     420
aaagaacacc tccttggaaatg gctngccgt cctcgccnt tgggtggnnnc gcntnccttt     480
t                                         481

<210> 86
<211> 472
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(472)
<223> n = A,T,C or G

<400> 86
aacatcttcc tgtataatgc tgtgtatcgatn cgatccgatn ttgtctgtg agaattcatt      60
acttggaaaa gcaacttnaa gcctggacac tggattaaa attcacaata tgcaacactt     120
taaacagtgt gtcaatctgc tcccttactt tgcgtatcacc agtctggaa taagggtatg     180
ccctattc acctgttaaa agggcgctaa gcattttga ttcaacatct ttttttttga     240
cacaagtccg aaaaaagcaa aagtaaacag ttnttaattt gtttagccat tcactttctt     300
catgggacac agccatttga tttaaaaagc aaattgcata atattgagct ttgggagctg     360
atatntgagc ggaagantag cctttctact tcaccagaca caactccctt catattggga     420
tgttnacnaa agttatgtct cttacagatg ggtatgtttt gtggcaattc tg                                         472

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<210> 87
<211> 413
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(413)
<223> n = A,T,C or G

<400> 87
agaaaccagt atctctnaaa acaacctctc ataccttgtg gacctaattt ttttgtgcgtg      60
tttgtgtgcg cgcataattat atagacaggc acatctttt tacttttgta aaagcttatg      120
ccctctttgtt atctatatct gtgaaagttt taatgatctg ccataatgtc ttggggacct      180
tttgtcttcgt tgtaaatggt actagagaaa acacctatnt tatgagtc aaactgttngt      240
tttattcgac atgaaggaaa ttccagatn acaacactna caaactctcc cttgactagg      300
ggggacaaag aaaagcanaa ctgaacatna gaaacaattt cctggtgaga aatncataa      360
acagaaattt ggtngtatat tgaaananng catcattnaa acgtttttt ttt      413

<210> 88
<211> 448
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(448)
<223> n = A,T,C or G

<400> 88
cgcagcgggt cctcttatac tagctccagc ctctcgctg ccccactccc cgctgtccgc      60
gtccttagccn accatggccg ggccccctgcg cgccccogctg ctccctgctgg ccatacctggc      120
cgtggccctgt gccgtgagcc ccgcggccgg ctccagatccc ggcaagccgc cgccctggt      180
gggaggccca tggaccccgc gtggaaagaag aagggtgtgctg gcgtgeactg gactttgccg      240
tcggcnanta caacaaaccc gcaacnactt ttacccnagcn cgccgtgcag gttgtgccgc      300
cccaancaaa ttgttactng gggtaantaa ttcttggaaag ttgaacctgg gccaaacnng      360
tttaccagaa ccnagccaaat tngaacaatt nccctccat aacagccccct tttaaaaagg      420
gaancantcc tgntctttc caaatttt      448

<210> 89
<211> 463
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(463)
<223> n = A,T,C or G

<400> 89
gaattttgtg cactggccac tgtgtatggaa ccattgggcc aggatgctt gagtttatca      60

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gtagtgattc tgccaaagtt ggtgtttaa catgagtatg taaaatgtca aaaaatttagc	120
agaggtctag gtctgcatac cagcagacag tttgtccgtg tatttttagt ctttgaagtt	180
ctcagtgaca agttnnttct gatgcgaagt tctnattcca gtgttttagt ctttgcac	240
tttnatgttn agacttgctt ctntnaaatt gctttgtnt tctgcaggta ctatctgtgg	300
ttaacaaaaa tagaannact tctctgcttn gaanatttga atatcttaca tctnaaaatn	360
aattctctcc ccatannaaa acccangccc ttgganaat ttgaaaaang gntccttcnn	420
aattcnnana anttcagnn tcataacaaca naacngganc ccc	463
<210> 90	
<211> 400	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1)...(400)	
<223> n = A,T,C or G	
<400> 90	
agggattgaa ggtctnttnt actgtcgac ttttcancac ccaactctac aagttgctgt	60
cttccactca ctgtctgttaa gcntnttaac ccagactgtt tcttcataaa tagaacaat	120
tcttcaccag tcacatcttc taggaccttt ttggattcag ttagtataag ctcttccact	180
tcctttgtta agacttcattc tggtaaagtc ttaagtttt tagaaaggaa tttaattgct	240
cgttctctaa caatgtcctc tccttgaagt atttggctga acaaccacc tnaagtcct	300
ttgtgcattcc attttaaata tacttaatag ggcattggtn cactaggta aattctgcaa	360
gagtcattctg tctgcaaaag ttgcgttagt atatctgcca	400
<210> 91	
<211> 480	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1)...(480)	
<223> n = A,T,C or G	
<400> 91	
gagctcgat ccaataatct ttgtctgagg gcagcacaca tatncagtgc catggnaact	60
ggcttaccccc acatgggagc agcatgcgt agntatataa ggtcattccc tgagtca	120
atgcctctt gactaccgtg tgccagtgt ggtgatttcc acacacctcc nnccgctt	180
tgtggaaaaa ctggcacttg nctggaaacta gcaagacatc acttacaaat tcacccacga	240
gacacttgaa aggtgttaca aagcgactct tgcattgtt tttgtccctc cgccaccagt	300
tgtcaataact aacccgctgg tttgccttca tcacattgtt gatctgttagc tctggataca	360
tctcctgaca gtactgaaga acttcttctt ttgtttcaaa agcaactctt ggtgcctgtt	420
ngatcagggtt cccatttccc agtccgaatg ttcacatggc atatnttact tcccacaaaa	480
<210> 92	
<211> 477	
<212> DNA	
<213> Homo sapien	

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<220>
<221> misc_feature
<222> (1)...(477)
<223> n = A,T,C or G

<400> 92
atacagccca natcccacca cgaagatgcg cttgttgact gagaacctga tgcggtcact      60
ggtccccgtg tagccccaggc gactctccac ctgctggaaag cggttcatgc tgcaactcctt    120
ccccacgcagg cagcagcggg gccggtaaat gaactccact cgtggcttgg gggttgcacggt    180
taantgcagg aagaggctga ccacctcgcg gtccaccagg atgcccact gtgcgggacc      240
tgcagcggaaa ctcctcgatg gtcatgagcg ggaagcgaat gangcccagg gccttgc当地    300
gaaccttccg cctgttctct ggcgtcacct gcagctgctg ccgctnacac tcggcctcg      360
accagcggac aaacggcggtt gaacagccgc acctcacgga tgcccantgt gtcgcgctcc    420
aggaacggcn ccagcgtgtc caggtcaatg tcggtaanc ctccgc当地 gatggcg      477

<210> 93
<211> 377
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(377)
<223> n = A,T,C or G

<400> 93
gaacggctgg accttgcctc gcattgtgct gctggcagga ataccttggc aagcagctcc      60
agtcccgagca gccccagacc gctgccccc gaagctaagc ctgcctctgg ccttccccctc    120
cgcctcaatg cagaaccant agtgggagca ctgtgttttag agttaagagt gaacactgtn    180
tgattttact tgggaatttc ctctgttata tagctttcc caatgctaatttccaaacaa      240
caacaacaaaa ataacatgtt tgctgttna gttgtataaaa agtangtgat tctgtatnta    300
aagaaaatatactactgttaca tatactgctt gcaanttctg tatttattgg tnctctggaa    360
ataaaatataat tattaaa                                         377

<210> 94
<211> 495
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(495)
<223> n = A,T,C or G

<400> 94
ccctttgagg ggtagggc cagttccag tggaaagaaac aggccaggag aantgcgtgc      60
cgagctgang cagattccc acagtgaccc cagagccctg ggctatagtc tctgaccctc    120
ccaaggaaag accaccttct ggggacatgg gctggagggc aggacctaga ggcaccaagg    180
gaaggccccca ttccggggct gttccccggag gaggaaaggga aggggctctg tgc当地      240
acgaggaana ggc当地tgcant cctggatca nacaccctt cacgtgtatc cccacacaaa    300

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tgcaagctca ccaaggccc ctctcagtcc cttccctaca ccctgaacgg ncactggccc	360
acacccaccc agancancca cccgccccatgg ggaatgtnc caaggaatcg cnngggcaacg	420
tggactctng tcccnnaagg gggcagaatc tccaatagan gganngaacc cttgctnana	480
aaaaaaaaana aaaaaa	495
<210> 95	
<211> 472	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1)...(472)	
<223> n = A,T,C or G	
<400> 95	
ggttacttgg tttcattgcc accacttagt ggatgtcatt tagaaccatt ttgtctgctc	60
cctctggaaag ccttgcgcag agcggacttt gtaattgttg gagaataact gctgaatttt	120
tagctgttt gagttgattc gcaccactgc accacaactc aatatgaaaa ctattnact	180
tatttatttat cttgtgaaaa gtataacaatg aaaattttgt tcataactgta tttatcaagt	240
atgatgaaaa gcaatagata tatattctt tattatgttn aattatgatt gccattatta	300
atcggcaaaa tgtggagtgt atgttcttt cacagtaata tatgccttt gtaacttcac	360
ttggttattt tattgtaaat gaattacaaa attcttaatt taagaaaaatg gtangttata	420
tttatttcan taatttctt cttgtttac gttaattttg aaaagaatgc at	472
<210> 96	
<211> 476	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1)...(476)	
<223> n = A,T,C or G	
<400> 96	
ctgaaggcatt tcttcaaact tntctacttt tgtcattgat acctgttagta agttgacaat	60
gtggtaaaat ttcaaaaatta tatgttaactt ctactagttt tactttctcc cccaaagtctt	120
ttttaactca tgattttac acacacaatc cagaacttat tatatagcct ctaagtcttt	180
attcttcaca gtagatgatg aaagagtccct ccagtgtctt gnngcanaatg ttctagntat	240
agctggatac atacngtggg agttctataa actcataacct cagtggact naaccaaaat	300
tgtgttagtc tcaattccta ccacactgag ggagcctccc aaatcactat attcttatct	360
gcaggtactc ctccagaaaa acngacaggg caggcttgca tgaaaaagtn acatctgcgt	420
tacaaagtct atttcctca nangtctgtn aagaacaat ttaatcttct agctt	476
<210> 97	
<211> 479	
<212> DNA	
<213> Homo sapien	
<220>	

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<221> misc_feature
<222> (1)...(479)
<223> n = A,T,C or G

<400> 97
actcttctta atgctgatata gatcttgagt ataagaatgc atatgtcact agaatggata      60
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caatcgcaaa tcaaaaactca caagtgcata tctgtttagt atttagtgttataaagactta      180
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<212> DNA

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tagcgggggt	aatatttat	actgtaaatg	agaatcaga	gtataatgtt	tatggtgaca	3300
aaattaaagg	cttcttata	tgtttaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	3360
aaaaaaaaara	aaaaaaaaaa	aaaaaaaaaa	aaaaaaataa	aaaaaaaaaa		3410

<210> 111
 <211> 1289
 <212> DNA
 <213> Homo sapien

<400> 111						
agccaggcgt	ccctctgcct	gcccactcag	tggcaacacc	cgggagctgt	tttgccttt	60
gtggagcctc	agcagttccc	tctttcagaa	ctcaactgcca	agagccctga	acaggagcca	120
ccatgcagt	cttcagctc	attaagacca	tgtatgatct	cttcaatttgc	ctcatcttcc	180
tgtgtgggtc	agccctgttgc	gcagtggc	tctgggtgtc	aatcgatggg	gcaccccttcc	240
tgaagatctt	cgggccactg	tcgtccagtg	ccatgcagtt	tgtcaacgtg	ggctacttcc	300
tcatcgacgc	cggcggtgt	gtctttgctc	ttgggttct	gggctgtat	gggtctaaga	360
ctgagagcaa	gtgtgcctc	gtgacgttct	tcttcatcc	cctcctcatac	ttcattgctg	420
aggttgcacgc	tgctgtggc	gccttgggt	acaccacaat	ggctgagcac	ttcctgacgt	480
tgctggtagt	gcctgccatc	aagaaagatt	atggttccca	ggaagacttc	actcaagtgt	540
ggaacaccac	catgaaaggg	ctcaagtgt	gtggcttcac	caactatacg	gattttgagg	600
actcaccctt	cttcaaagag	aacagtgcct	ttccccccatt	ctgttgcac	gacaacgtca	660
ccaaacacagc	caatgaaacc	tgcaccaagc	aaaaggctca	cgaccaaaaa	gtagagggtt	720
gcttcaatca	gctttgtat	gacatccgaa	ctaattgcagt	caccgtgggt	gggtgtggcag	780
ctgaaattgg	gggcctcgag	ctggctgcca	tgattgtgtc	catgtatctg	tactgcaatc	840
tacaataagt	ccacttctgc	ctctgcaact	actgctgcca	catggaaact	gtgaagaggc	900
accctggcaa	gcagcagtga	ttgggggagg	ggacaggatc	taacaatgtc	acttgggcca	960
aatggacact	gccccttctg	ctccagactt	ggggctagat	agggaccact	ccttttagcg	1020
atgcctgact	ttccttccat	tgggtgggtgg	atgggtgggg	ggcattccag	agcctctaag	1080
gtagccagtt	ctgtgcccc	ttcccccaagt	ctattaaacc	cttgatatgc	cccttaggccc	1140

tagtggtgat cccagtgc	tactgggga tgagagaaag gcatttata gcctggcat	1200
aagtgaardc agcagagc	ctgggtggat gtgtagaagg cacttcaaaa tgcataaacc	1260
tgttacaatg ttaaaaaaaaaaa aaaaaaaaaa		1289

<210> 112
 <211> 315
 <212> PRT
 <213> Homo sapien

<400> 112			
Met Val Phe Thr Val Arg Leu Leu His Ile Phe Thr Val Asn Lys Gln			
1	5	10	15
Leu Gly Pro Lys Ile Val Ile Val Ser Lys Met Met Lys Asp Val Phe			
20	25	30	
Phe Phe Leu Phe Phe Leu Gly Val Trp Leu Val Ala Tyr Gly Val Ala			
35	40	45	
Thr Glu Gly Leu Leu Arg Pro Arg Asp Ser Asp Phe Pro Ser Ile Leu			
50	55	60	
Arg Arg Val Phe Tyr Arg Pro Tyr Leu Gln Ile Phe Gly Gln Ile Pro			
65	70	75	80
Gln Glu Asp Met Asp Val Ala Leu Met Glu His Ser Asn Cys Ser Ser			
85	90	95	
Glu Pro Gly Phe Trp Ala His Pro Pro Gly Ala Gln Ala Gly Thr Cys			
100	105	110	
Val Ser Gln Tyr Ala Asn Trp Leu Val Val Leu Leu Val Ile Phe			
115	120	125	
Leu Leu Val Ala Asn Ile Leu Leu Val Asn Leu Leu Ile Ala Met Phe			
130	135	140	
Ser Tyr Thr Phe Gly Lys Val Gln Gly Asn Ser Asp Leu Tyr Trp Lys			
145	150	155	160
Ala Gln Arg Tyr Arg Leu Ile Arg Glu Phe His Ser Arg Pro Ala Leu			
165	170	175	
Ala Pro Pro Phe Ile Val Ile Ser His Leu Arg Leu Leu Leu Arg Gln			
180	185	190	
Leu Cys Arg Arg Pro Arg Ser Pro Gln Pro Ser Ser Pro Ala Leu Glu			
195	200	205	
His Phe Arg Val Tyr Leu Ser Lys Glu Ala Glu Arg Lys Leu Leu Thr			
210	215	220	
Trp Glu Ser Val His Lys Glu Asn Phe Leu Leu Ala Arg Ala Arg Asp			
225	230	235	240
Lys Arg Glu Ser Asp Ser Glu Arg Leu Lys Arg Thr Ser Gln Lys Val			
245	250	255	
Asp Leu Ala Leu Lys Gln Leu Gly His Ile Arg Glu Tyr Glu Gln Arg			
260	265	270	
Leu Lys Val Leu Glu Arg Glu Val Gln Gln Cys Ser Arg Val Leu Gly			
275	280	285	
Trp Val Ala Glu Ala Leu Ser Arg Ser Ala Leu Leu Pro Pro Gly Gly			
290	295	300	
Pro Pro Pro Asp Leu Pro Gly Ser Lys Asp			
305	310	315	

<210> 113
 <211> 553
 <212> PRT
 <213> Homo sapien

<400> 113
 Met Val Gln Arg Leu Trp Val Ser Arg Leu Leu Arg His Arg Lys Ala
 1 5 10 15
 Gln Leu Leu Leu Val Asn Leu Leu Thr Phe Gly Leu Glu Val Cys Leu
 20 25 30
 Ala Ala Gly Ile Thr Tyr Val Pro Pro Leu Leu Leu Glu Val Gly Val
 35 40 45
 Glu Glu Lys Phe Met Thr Met Val Leu Gly Ile Gly Pro Val Leu Gly
 50 55 60
 Leu Val Cys Val Pro Leu Leu Gly Ser Ala Ser Asp His Trp Arg Gly
 65 70 75 80
 Arg Tyr Gly Arg Arg Pro Phe Ile Trp Ala Leu Ser Leu Gly Ile
 85 90 95
 Leu Leu Ser Leu Phe Leu Ile Pro Arg Ala Gly Trp Leu Ala Gly Leu
 100 105 110
 Leu Cys Pro Asp Pro Arg Pro Leu Glu Leu Ala Leu Leu Ile Leu Gly
 115 120 125
 Val Gly Leu Leu Asp Phe Cys Gly Gln Val Cys Phe Thr Pro Leu Glu
 130 135 140
 Ala Leu Leu Ser Asp Leu Phe Arg Asp Pro Asp His Cys Arg Gln Ala
 145 150 155 160
 Tyr Ser Val Tyr Ala Phe Met Ile Ser Leu Gly Gly Cys Leu Gly Tyr
 165 170 175
 Leu Leu Pro Ala Ile Asp Trp Asp Thr Ser Ala Leu Ala Pro Tyr Leu
 180 185 190
 Gly Thr Gln Glu Glu Cys Leu Phe Gly Leu Leu Thr Leu Ile Phe Leu
 195 200 205
 Thr Cys Val Ala Ala Thr Leu Leu Val Ala Glu Glu Ala Ala Leu Gly
 210 215 220
 Pro Thr Glu Pro Ala Glu Gly Leu Ser Ala Pro Ser Leu Ser Pro His
 225 230 235 240
 Cys Cys Pro Cys Arg Ala Arg Leu Ala Phe Arg Asn Leu Gly Ala Leu
 245 250 255
 Leu Pro Arg Leu His Gln Leu Cys Cys Arg Met Pro Arg Thr Leu Arg
 260 265 270
 Arg Leu Phe Val Ala Glu Leu Cys Ser Trp Met Ala Leu Met Thr Phe
 275 280 285
 Thr Leu Phe Tyr Thr Asp Phe Val Gly Glu Gly Leu Tyr Gln Gly Val
 290 295 300
 Pro Arg Ala Glu Pro Gly Thr Glu Ala Arg Arg His Tyr Asp Glu Gly
 305 310 315 320
 Val Arg Met Gly Ser Leu Gly Leu Phe Leu Gln Cys Ala Ile Ser Leu
 325 330 335
 Val Phe Ser Leu Val Met Asp Arg Leu Val Gln Arg Phe Gly Thr Arg
 340 345 350
 Ala Val Tyr Leu Ala Ser Val Ala Ala Phe Pro Val Ala Ala Gly Ala

355	360	365
Thr Cys Leu Ser His Ser Val Ala Val Val Thr Ala Ser Ala Ala Leu		
370	375	380
Thr Gly Phe Thr Phe Ser Ala Leu Gln Ile Leu Pro Tyr Thr Leu Ala		
385	390	395
Ser Leu Tyr His Arg Glu Lys Gln Val Phe Leu Pro Lys Tyr Arg Gly		400
405	410	415
Asp Thr Gly Gly Ala Ser Ser Glu Asp Ser Leu Met Thr Ser Phe Leu		
420	425	430
Pro Gly Pro Lys Pro Gly Ala Pro Phe Pro Asn Gly His Val Gly Ala		
435	440	445
Gly Gly Ser Gly Leu Leu Pro Pro Pro Ala Leu Cys Gly Ala Ser		
450	455	460
Ala Cys Asp Val Ser Val Arg Val Val Val Gly Glu Pro Thr Glu Ala		
465	470	475
Arg Val Val Pro Gly Arg Gly Ile Cys Leu Asp Leu Ala Ile Leu Asp		480
485	490	495
Ser Ala Phe Leu Leu Ser Gln Val Ala Pro Ser Leu Phe Met Gly Ser		
500	505	510
Ile Val Gln Leu Ser Gln Ser Val Thr Ala Tyr Met Val Ser Ala Ala		
515	520	525
Gly Leu Gly Leu Val Ala Ile Tyr Phe Ala Thr Gln Val Val Phe Asp		
530	535	540
Lys Ser Asp Leu Ala Lys Tyr Ser Ala		
545	550	

<210> 114
 <211> 241
 <212> PRT
 <213> Homo sapien

<400> 114		
Met Gln Cys Phe Ser Phe Ile Lys Thr Met Met Ile Leu Phe Asn Leu		
1	5	10
Leu Ile Phe Leu Cys Gly Ala Ala Leu Leu Ala Val Gly Ile Trp Val		
20	25	30
Ser Ile Asp Gly Ala Ser Phe Leu Lys Ile Phe Gly Pro Leu Ser Ser		
35	40	45
Ser Ala Met Gln Phe Val Asn Val Gly Tyr Phe Leu Ile Ala Ala Gly		
50	55	60
Val Val Val Phe Ala Leu Gly Phe Leu Gly Cys Tyr Gly Ala Lys Thr		
65	70	75
80		
Glu Ser Lys Cys Ala Leu Val Thr Phe Phe Ile Leu Leu Ile		
85	90	95
Phe Ile Ala Glu Val Ala Ala Val Val Ala Leu Val Tyr Thr Thr		
100	105	110
Met Ala Glu His Phe Leu Thr Leu Leu Val Val Pro Ala Ile Lys Lys		
115	120	125
Asp Tyr Gly Ser Gln Glu Asp Phe Thr Gln Val Trp Asn Thr Thr Met		
130	135	140
Lys Gly Leu Lys Cys Cys Gly Phe Thr Asn Tyr Thr Asp Phe Glu Asp		

145	150	155	160
Ser Pro Tyr Phe Lys Glu Asn Ser Ala Phe Pro Pro Phe Cys Cys Asn			
165	170	175	
Asp Asn Val Thr Asn Thr Ala Asn Glu Thr Cys Thr Lys Gln Lys Ala			
180	185	190	
His Asp Gln Lys Val Glu Gly Cys Phe Asn Gln Leu Leu Tyr Asp Ile			
195	200	205	
Arg Thr Asn Ala Val Thr Val Gly Gly Val Ala Ala Gly Ile Gly Gly			
210	215	220	
Leu Glu Leu Ala Ala Met Ile Val Ser Met Tyr Leu Tyr Cys Asn Leu			
225	230	235	240
Gln			

<210> 115
<211> 366
<212> DNA
<213> Homo sapien

<400> 115	
gctctttc tc cccctc tca tgaat ttaat tcttc aact tgcaat ttgc aaggattaca	60
cattt cactg tgatgtat atgtgttgc aa aaaaaaaaaa gtgtcttgc ttaaaattac	120
ttggtttgc aatccatctt gcttttccc cattggaa ct agtcattaa ac ccatctctga	180
actggtagaa aa acatctga agagctagtc tatcagcatc tgacaggta attggatgg	240
tctcagaacc atttcaccca gacagcctgt ttctatcctg tttaataaa at tagttgggt	300
tctctacatg cataacaaac cctgctccaa tctgtcacat aaaagtctgt gacttgaagt	360
tttagtc	366

<210> 116
<211> 282
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(282)
<223> n = A,T,C or G

<400> 116	
acaaagatga accat ttcct atattatagc aaaat taaa tctaccgta ttcta atatt	60
gagaaatgag atnaaacaca atnttataaa gtctacttag agaagatcaa gtgacctcaa	120
agactttact atttcataat tttaagacac atgatttac ctat tttatg aacctggttc	180
atacgtaaaa caaaggataa tgtgaacagc agagaggatt tggcaga aaatctatgt	240
tcaatctnga actatctana tcacagacat ttctattcct tt	282

<210> 117
<211> 305
<212> DNA
<213> Homo sapien

<220>

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<221> misc_feature
<222> (1)...(305)
<223> n = A,T,C or G

<400> 117
acacatgtcg ctcaactgcc ttcttagatg ctctggtca acatanagga acagggacca      60
tatttatcct ccctcctgaa acaaattgcaa aataanacaa aatatatgaa acaattgcaa      120
aataaggcaa aatatatgaa acaacaggc tcgagatatt ggaaatcagt caatgaagga      180
tactgtatccc tgatcactgt cctaattgcag gatgtggaa acagatgagg tcacctctgt      240
gactgccccca gcttactgcc tgttagagat ttctangctg cagttcagac agggagaaat      300
tgggt      305

<210> 118
<211> 71
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(71)
<223> n = A,T,C or G

<400> 118
accaagggtgt ntgaatctct gacgtgggaa tctctgattc ccgcacaatc tgagtggaaa      60
aantcctggg t      71

<210> 119
<211> 212
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(212)
<223> n = A,T,C or G

<400> 119
actccgggtt gtgtcagcag cacgtggcat tgaacatngc aatgtggagc ccaaaccaca      60
gaaaatgggg taaaattggc caactttcta tnaactttag ttggcaant tgccaccaac      120
agtaagctgg cccttctaat aaaagaaaaat taaaaggttt ctcactaanc ggaattaant      180
aatggantca aganactccc aggcctcagc gt      212

<210> 120
<211> 90
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(90)
<223> n = A,T,C or G

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<400> 120		
actcggttgc a natcaggggc cccccagagt caccgttgca ggagtccttc tggtcttgcc	60	
ctccgcggc gcagaacatg ctgggggttgt	90	
<210> 121		
<211> 218		
<212> DNA		
<213> Homo sapien		
<220>		
<221> misc_feature		
<222> (1)...(218)		
<223> n = A,T,C or G		
<400> 121		
tgtancgtga anacgacaga nagggttgc aaaaatggag aanccttcaa gtcattttga	60	
gaataagatt tgctaaaaga tttggggcta aaacatggtt attgggagac atttctgaag	120	
atatncangt aaattangga atgaattcat gggtctttt ggaattcctt tacgatngcc	180	
agcatanact tcatagtgggg atancagcta cccttgta	218	
<210> 122		
<211> 171		
<212> DNA		
<213> Homo sapien		
<400> 122		
taggggtgta tgcaactgta aggacaaaaa ttgagactca actggcttaa ccaataaagg	60	
catttggtag ctcatggAAC aggaagtccgg atggggggc atcttcagtg ctgcattgagt	120	
caccaccccg gcggggcat ctgtgccaca ggtccctgtt gacagtgcgg t	171	
<210> 123		
<211> 76		
<212> DNA		
<213> Homo sapien		
<220>		
<221> misc_feature		
<222> (1)...(76)		
<223> n = A,T,C or G		
<400> 123		
tgttagcgtga agacnacaga atggtgtgtg ctgtgctatc caggaacaca tttattatca	60	
tttatcaanta ttgtgt	76	
<210> 124		
<211> 131		
<212> DNA		
<213> Homo sapien		
<400> 124		

acctttcccc aaggccaatg tcctgtgtgc taactggccg gctgcaggac agctgcaatt	60
caatgtgtcg ggtcatatgg aggggaggag actctaaaat agccaatttt attctcttgg	120
ttaagatttg t	131
<210> 125	
<211> 432	
<212> DNA	
<213> Homo sapien	
<400> 125	
acttttatcta ctggctatga aatagatggt ggaaaattgc gttaccaact ataccactgg	60
cttgcggaaatgg aggtgatagc tcttcagagg acttgtgact tttgctcaga tgctgaagaa	120
ctacagtctg catttggcag aaatgaagat gaatttggat taaatgagga tgctgaagat	180
ttgcctcacc aaacaaaatgt gaaacaactg agagaaaattt ttcaggaaaa aagacagtgg	240
ctcttgaagt atcagtcaact tttgagaatg tttcttagtt actgcataact tcattggatcc	300
catggtgggg gtctgcattc tgtaagaatg gaatttgattt tgctttgca agaatctcag	360
caggaaacat cagaaccact attttcttagc cctctgtcag agcaaaccctc agtgcctctc	420
ctctttgctt gt	432
<210> 126	
<211> 112	
<212> DNA	
<213> Homo sapien	
<400> 126	
acacaacttg aatagtaaaa tagaaactga gctgaaattt ctaattcact ttcttaaccat	60
agtaagaatg atatttcccc ccagggatca ccaaataattt ataaaaattt gt	112
<210> 127	
<211> 54	
<212> DNA	
<213> Homo sapien	
<400> 127	
accacgaaac cacaaacaag atggaagcat caatccactt gccaaaggcaca gcag	54
<210> 128	
<211> 323	
<212> DNA	
<213> Homo sapien	
<400> 128	
acctcattag taattgtttt gttgtttcat tttttctaa tgtctccctt ctaccagctc	60
acctgagata acagaatgaa aatggaagga cagccagatt tctcatttgc tctctgctca	120
ttctctctga agtcttagtt acccattttg gggaccattt ataggcaata aacacagttc	180
ccaaaggcatt tggacagttt cttgttgtgt ttttagaatgg ttttcctttt tcttagcctt	240
ttcctgcaaa aggctcactc agtcccttgc ttgctcagtg gactgggctc cccagggcct	300
aggctgcctt cttttccatg tcc	323
<210> 129	
<211> 192	

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<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(192)
<223> n = A,T,C or G

<400> 129
acatacatgt gtgtatattt ttaaatatca ctttgtatc actctgactt tttgcatac      60
tggaaacaca ctaacataat ttntgtaac catgatcaga tacaaccacaa atcattcatc    120
tagcacattc atctgtgata naaagatagg tgagttcat ttccttcacg ttggccatg     180
gataaaacaaa gt                                192

<210> 130
<211> 362
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(362)
<223> n = A,T,C or G

<400> 130
cccttttta tggaaatgagt agactgtatg tttgaanatt tanccacaac ctcttgaca      60
tataatgacg caacaaaaag gtgctgtta gtcctatgggt tcagtttatg cccctgacaa    120
gtttccattt tggtttgccg atcttctggc taatcggtt atcctccatg ttatttagtaa   180
ttctgtattt cattttgtta acgcctgta gatgtaccc gctangaggc taactttata    240
cttattttaa agcttttatt ttgtggtcat taaaatggca atttatgtgc agcactttat  300
tgcagcagga agcacgtgtg gggtgggtgt aaagctttt gctaatttta aaaagtaatg  360
gg                                362

<210> 131
<211> 332
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(332)
<223> n = A,T,C or G

<400> 131
cttttggaa gatcggttcc actcctgtgg acatcttgg ttaatggagt ttcccatgca      60
gtangactgg tatgggtgca gctgtccaga taaaaacatt tgaagagctc caaaatgaga    120
gttctccctg gttccctgt ctgtccaa gtcctggc agcctttt aggaggcato     180
ttctgtactt gattaaggca gcttgtaat ctgtatgtat ttgggttttattt atccactaa  240
cttccatctg ttatcactgg agaaagccca gactccccan gacnggtacg gattgtgggc  300
atanaaggat tgggtgaagc tggcggtgtg gt                                332

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<210> 132
<211> 322
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(322)
<223> n = A,T,C or G

<400> 132
acttttgcctttttgtatataaaacaatcttgggacatttcctgaaaaatgggtgtcc
agtggctaaggaaactcgatttcaagcaattctgaaaggaaaccaggcatgacacagaat
ctcaaattcccaaacaggggctctgtgggaaaatgagggaggaccttttatctcggtt
tttagcaagttaaaatgaanatgacaggaaaggcttatttatcaacaaagagaagagttt
ggatgcttctaaaaaaaactttggtagagaaaataggaatgctnaatcctaggaaagcct
gtaacaatctacaattggtc ca 60

<210> 133
<211> 278
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(278)
<223> n = A,T,C or G

<400> 133
acaaggccttcaaaatgggattaatctttctgtantttatctgcataatttttttc
tttccatctgttcctgggttgacaatttgggaaacaactctattgcataataaaaaa
aaaatcacaaatcttcctttaagctatgtttaattcaactattcctgttattcgtt
tttgcataatgggtttgtcaagaaattatattttcaaaatatgtntattttttgtatgggt
cccacgaaacactaataaaaaaccacagaga ccagcctg 120

<210> 134
<211> 121
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(121)
<223> n = A,T,C or G

<400> 134
gtttaaaaatggtttgc tccatagagg aaagaatgtt aaactttgtatttaaaaca
tgattctctg aggttaaact tggtttcaa atgttatttt tacttgtattttgtt
t 120

<210> 135

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<211> 350		
<212> DNA		
<213> Homo sapien		
<220>		
<221> misc_feature		
<222> (1)...(350)		
<223> n = A,T,C or G		
<400> 135		
acttanaacc atgcctagca catcagaatc cctcaaagaa catcagtata atccataacc	60	
atancaagtg gtgactgggt aagcgtgcga caaaggtagtgc ctggcacatt acttgtgtgc	120	
aaacttgata ctttgttct aagttagaac tagtatacag tnccttaggan tggtaactcca	180	
gggtgccccca caactcctgc agccgctccct ctgtgccagn ccctgnaagg aactttcgct	240	
ccacacctaat caagccctgg gccatgtac ctgcaattgg ctgaacaaaac gtttgctgag	300	
ttcccaagga tgcaaaggct ggtgctcaac tcctggggcg tcaactcagt	350	
<210> 136		
<211> 399		
<212> DNA		
<213> Homo sapien		
<220>		
<221> misc_feature		
<222> (1)...(399)		
<223> n = A,T,C or G		
<400> 136		
tgtaccgtga agacgacaga agttgcatgg cagggacagg gcagggccga ggccagggtt	60	
gctgtgattt tatccgata ntccctgtga gaaaagataa tgagatgacg tgacgacgc	120	
gcagacttgt gtctgccttc aanaagccag acaggaaggc cctgcctgcc ttggctctga	180	
cctggccggcc agccagccag ccacaggtgg gcttcttc tttgtggtga caacnccaag	240	
aaaactgcag aggcccaggg tcaggtgtta gtgggtangt gaccataaaa caccaggtgc	300	
tcccaggaac ccgggcaaaag gccatccca cctacagcca gcatgcccac tggcgtgatg	360	
ggtgcagang gatgaagcag ccagntttc tgctgtgg	399	
<210> 137		
<211> 165		
<212> DNA		
<213> Homo sapien		
<220>		
<221> misc_feature		
<222> (1)...(165)		
<223> n = A,T,C or G		
<400> 137		
actgggtgtgg tnggggggtga tgctgggtt anaagttgan gtgacttcan gatgggtgtgt	60	
ggaggaagtg tgtgaacgtt gggatgtaga nttttggcc gtgctaaatg agcttcggga	120	
ttggctggtc ccactgggtgg tcactgtcat tggtgggtt cctgt	165	

<210> 138		
<211> 338		
<212> DNA		
<213> Homo sapien		
<220>		
<221> misc_feature		
<222> (1)...(338)		
<223> n = A,T,C or G		
<400> 138		
actcaactgga atgccacatt cacaacagaa tcagaggctc gtgaaaacat taatggctcc	60	
ttaacttctc cagtaagaat cagggacttg aaatggaaac gttaacagcc acatgcccaa	120	
tgctggcag tctccatgc cttccacagt gaaaggcgtt gagaaaaatc acatccaatg	180	
tcatgtgtt ccagccacac caaaaggtgc ttggggtgga gggctggggg catananggt	240	
cangcctcag gaagcctcaa gttccattca gcttgcac tgcattcc ccatntttaa	300	
aaaaactgat gcctttttt ttttttttg taaaattc	338	
<210> 139		
<211> 382		
<212> DNA		
<213> Homo sapien		
<400> 139		
gggaatcttg gttttggca tctggttgc ctatagccga ggccactttg acagaacaaa	60	
gaaaggact tcgagtaaga aggtgattt cagccagcct agtccccaa gtgaaggaga	120	
attcaaacag acctcgcat tcctgggtg agcctggcgt gctcaccgccc tatcatctgc	180	
atttgcccta ctcaggtgct accggactct ggcccctgat gtctgttagtt tcacaggatg	240	
ccttatttgt ctttacacc ccacaggccc ccctacttct tcggatgtgt ttttataat	300	
gtcagctatg tgcccatcc tccttcatgc cctccctccc ttccatcca ctgctgatg	360	
gcctggaact tgtttaagt gt	382	
<210> 140		
<211> 200		
<212> DNA		
<213> Homo sapien		
<220>		
<221> misc_feature		
<222> (1)...(200)		
<223> n = A,T,C or G		
<400> 140		
accaaancctt ctttctgttg tgtngattt tactataggg gtttngcttn ttctaaanat	60	
acttttcatt taacanctt tgttaagtgt caggtgcac tttgctccat anaattattg	120	
ttttcacatt tcaacttgta tgtgtttgtc tcttanagca ttggtaaat cacatatttt	180	
atattcagca taaaggagaa	200	
<210> 141		
<211> 335		
<212> DNA		

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(335)

<223> n = A,T,C or G

<400> 141

actttatTTT	caaaacactc	atatgttgcA	aaaaacacat	agaaaaataa	agtttggtgg	60
gggtgctgac	tAAacttcaa	gtcacagact	tttatgtgac	agattggagc	agggtttgtt	120
atgcATgtAG	agaACccAAA	ctaatttatt	aaacaggata	gaaacaggct	gtctgggtga	180
aatggTTctg	agaaccatcc	aattcacCTG	tcagatgctg	atanactAGC	tcttcagatg	240
tttttctacc	agttcagaga	tnggttaatg	actanttcca	atggggaaaa	agcaagatgg	300
attcacaAAAC	caagtaattt	taaacaAAAGA	cactt			335

<210> 142

<211> 459

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(459)

<223> n = A,T,C or G

<400> 142

accaggttaa	tattGCCACA	tatATCCttt	ccaattgcgg	gctaaacaga	cgtgtattta	60
gggtgttta	aAGACAACCC	agcttaatAT	caagagaaat	tgtgaccTTT	catggagtat	120
ctgatggaga	aaACACTGAG	ttttgacAAA	tcttattttA	ttcagatAGC	agtctgtatCA	180
cacatggtcc	aaACAACACTC	aaATAATAAA	tcaaataATNA	tcagatgtta	aagattggTC	240
ttcaaacatc	atAGCCAATG	atgccccGCT	tgcctataAT	ctctccgaca	taaaaccaca	300
tcaacacCTC	agtggccACC	aaaccattca	gcacagCTC	cttaactGTG	agctgttGA	360
agctaccagt	ctgagcactA	ttgactatNT	ttttcangCT	ctgaataGCT	ctagggatCT	420
cagcangggT	gggaggaACC	agctcaacct	tggcgtANT			459

<210> 143

<211> 140

<212> DNA

<213> Homo sapien

<400> 143

acatttcctt	ccaccaagTC	aggactcCTG	gcttctgtgg	gagttcttat	cacctgaggg	60
aaatccaaAC	agtctctcCT	agaaAGGAAT	agtgtcacca	accccaccca	tctccctgag	120
accatccgac	ttccctgtgt					140

<210> 144

<211> 164

<212> DNA

<213> Homo sapien

<220>

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<221> misc_feature
<222> (1)...(164)
<223> n = A,T,C or G

<400> 144
acttcagtaa caacatacaa taacaacatt aagtgtatat tgccatctt gtcattttct      60
atctataccca ctctcccttc tgaaaacaan aatcactanc caatcactta tacaatattg      120
aggcaattaa tccatatttgc ttttcaataa ggaaaaaaag atgt                         164

<210> 145
<211> 303
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(303)
<223> n = A,T,C or G

<400> 145
acgttagacca tccaaactttg tatttgtaat ggcaaacatc cagnagaat tcctaaacaa      60
actggagggt atttataccca aattatccca ttcattaaca tgccctccctc ctcaggctat      120
gcaggacagc tatcataagt cggcccaggc atccagatac taccatttgt ataaacttca      180
gtaggggagt ccatccaagt gacaggtcta atcaaaggag gaaatggaac ataagcccag      240
tagtaaaatn ttgcttagct gaaacagcca caaaagactt accgccgtgg tgattaccat      300
caa                                         303

<210> 146
<211> 327
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(327)
<223> n = A,T,C or G

<400> 146
actgcagctc aattagaagt ggtctctgac tttcatcanc ttctccctgg gctccatgac      60
actggcctgg agtgactcat tgctctggtt ggttgagaga gctccttgc caacaggcct      120
ccaagtcaagg gctgggattt gtttccttgc cacattctag caacaatatg ctggccactt      180
cctgaacagg gagggtgaaa ggagccagca tggaacaagc tgccacttgc taaagttagcc      240
agacttgccc ctgggcctgt cacacctact gatgaccttc tgtgcctgca ggatggaatg      300
taggggtgag ctgtgtgact ctatgggt                                327

<210> 147
<211> 173
<212> DNA
<213> Homo sapien

<220>

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<221> misc_feature
<222> (1)...(173)
<223> n = A,T,C or G

<400> 147
acattgttt tttgagataa agcattgana gagctctcct taacgtgaca caatggaagg      60
actggAACAC atacccacat ctttGTTCTG aggataatt ttctgataaa gtcttgctgt      120
atattcaAGC acatATgttA tatattattc agtccatgt ttatAGCCTA gtt      173

<210> 148
<211> 477
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(477)
<223> n = A,T,C or G

<400> 148
acaaccactt tatctcatcg aatttttaac ccaaactcac tcacttgcc tttctatcct      60
atgggatata ttatttgatg ctccatttca tcacacatat atgaataata cactcatact      120
gccctactac ctgctgcaat aatcacattc ccttcctgtc ctgaccctga agccattggg      180
gtgttcctag tggccatcg tccangcctg caccttgagc ccttgagctc cattgctcac      240
nccancccac ctcaccgacc ccattcctt acacagctac ctccctgctc tctaacccca      300
tagatttatnt ccaaattcag tcaattaagt tactattaac actctacccg acatgtccag      360
caccacttgtt aaggcattcgc cagccaaacac acacacacac acacncacac acacacatat      420
ccaggcacag gtcacccatc cttcacaatc acccctttaa ttaccatgct atggtgg      477

<210> 149
<211> 207
<212> DNA
<213> Homo sapien

<400> 149
acagttgtat tataatatca agaaataaac ttgcaatgag agcatttaag aggaaagaac      60
taacgtattt tagagagcca aggaaggTTT ctgtggggag tgggatgtaa ggtggggcct      120
gatgataaat aagagtcaGC caggtaagtG ggtgggtgtgg tatgggcaca gtgaagaaca      180
tttcaggcag agggAACAGC agtgaaa      207

<210> 150
<211> 111
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(111)
<223> n = A,T,C or G

<400> 150

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accttgattt cattgctgct ctgatggaaa cccaaactatc taattttagct aaaacatggg	60
cacttaaatg tggtcagtgt ttggacttgt taactantgg catctttggg t	111
<210> 151	
<211> 196	
<212> DNA	
<213> Homo sapien	
<400> 151	
agcgccgcag gtcataattga acattccaga taccttatcat tactcgatgc tggtgataac	60
agcaagatgg cttaactc agggtcacca ccagctattg gaccttacta tgaaaaccat	120
ggataccaac cgaaaaaccc ctatcccga cagcccactg tggccccac tgtctacgag	180
gtgcattccgg ctcagt	196
<210> 152	
<211> 132	
<212> DNA	
<213> Homo sapien	
<400> 152	
acagcacttt cacatgttaag aagggagaaa ttccataatg taggagaaag ataacagaac	60
cttccccctt tcatacttagt gtggaaacct gatgtttat gttgacagga atagaaccag	120
gagggagttt gt	132
<210> 153	
<211> 285	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1)...(285)	
<223> n = A,T,C or G	
<400> 153	
acaanaccca nganaggcca ctggccgtgg tgtcatggcc tccaaacatg aaagtgtcag	60
cttctgctct tatgtcctca tctgacaact ctttaccatt tttatcctcg ctcagcagga	120
gcacatcaat aaagtccaaa gtcttgact tggccttggc ttggaggaag tcatacacac	180
cctggctagt gaggggtgcgg cgccgctcct ggatgacggc atctgtgaag tcgtgcacca	240
gtctgcaggc cctgtggaag cgccgtccac acggagtnag gaatt	285
<210> 154	
<211> 333	
<212> DNA	
<213> Homo sapien	
<400> 154	
accacagtcc tggggccca gggcttcatg accctttctg tgaaaagcca tattatcacc	60
accccaaatt tttccttaaa tatcttaac tgaagggtc agcctcttga ctgcaaagac	120
cctaagccgg ttacacagct aactcccact ggccctgatt tggaaattt ctgctgcctg	180
attggcacag gagtcgaagg tggtcagtc ccctcctcgg tggaaacgaga ctctgattt	240

agtttcacaa atttcgggc cacctcgta ttgctcctct gaaataaaat ccggagaatg gtcaggcctg tctcatccat atggatcttc cgg	300 333
<210> 155	
<211> 308	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1)...(308)	
<223> n = A,T,C or G	
<400> 155	
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<210> 156	
<211> 295	
<212> DNA	
<213> Homo sapien	
<400> 156	
accttgctcg gtgcttggaa catattagga actcaaaata tgagatgata acagtgccta ttattgatta ctgagagaac tggtagacat ttagttgaag attttctaca caggaactga aataggaga ttatgtttgg ccctcatatt ctccctatc ctccctgcct cattctatgt ctaataatatt ctcaatcaa taaggttagc ataatcagga aatcgaccaa ataccaatat aaaaccagat gtctatcctt aagatttca aatagaaaac aaattaacag actat	60 120 180 240 295
<210> 157	
<211> 126	
<212> DNA	
<213> Homo sapien	
<400> 157	
acaagtttaa atagtgtgt cactgtgcat gtgctgaaat gtgaaatcca ccacattct gaagagcaaa acaaattctg tcatacatac tctatcttgg gtcgtggta tatctgtccc cttagt	60 120 126
<210> 158	
<211> 442	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1)...(442)	

<223> n = A,T,C or G

<400> 158

acccactgg	cttggaaaca	cccatccta	atacgatgat	ttttctgtcg	tgtgaaaatg	60
aanccagcag	gctgccccta	gtcagtccctt	ccttccagag	aaaaagagat	ttgagaaaagt	120
gcctggtaa	ttcaccatta	atttcctccc	ccaaactctc	tgagtcttcc	cttaatattt	180
ctgggtgttc	tgaccaaagc	aggtcatgg	ttgtttagca	tttggatcc	cagtgaaagta	240
natgtttgta	gcctgcata	cttagccctt	cccacgcaca	aacggagtgg	cagagtggtg	300
ccaaccctgt	tttcccagtc	cacgtagaca	gattcacagt	gcggaattct	ggaagctgga	360
nacagacggg	ctcttgcag	agccggact	ctgagangga	catgagggcc	tctgcctctg	420
tgttcattct	ctgatgtcct	gt				442

<210> 159

<211> 498

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1) ... (498)

<223> n = A,T,C or G

<400> 159

acttccagg	aacgttgtt	tttccgttga	gcctgaactg	atgggtgacg	tttaggttc	60
tccaaacaaga	actgagggtt	cagagcgggt	aggaagagt	gctgttccag	ttgcacctgg	120
gctgctgtgg	actgttgtt	attcctact	acggcccaag	gttgttggac	tggcanaaag	180
gtgtgttgg	gganttgagc	tcgggcggct	gtgttaggtt	gtgggctctt	caacaggggc	240
tgctgtggtg	ccgggangtg	aangtgtt	gtcaacttgag	cttggccagc	tctggaaagt	300
antanattct	tcctgaaggc	cagcgctgt	ggagctggca	ngggtcantg	ttgtgtgtaa	360
cgaaccagt	ctgctgtggg	tgggtgtana	tcctccacaa	agcctgaagt	tatgtgtcn	420
tcaggttana	atgtggtttc	agtgtccctg	ggcngctgtg	gaaggttgt	nattgtcacc	480
aaggaaataa	gctgtgg					498

<210> 160

<211> 380

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1) ... (380)

<223> n = A,T,C or G

<400> 160

acctgcattcc	agcttccctg	ccaaactcac	aaggagacat	caacctctag	acaggaaac	60
agcttcagga	tacttccagg	agacagagcc	accagcagca	aaacaaatat	tcccatgcct	120
ggagcatggc	atagaggaag	ctganaaatg	tgggtctga	ggaagccatt	ttagtctggc	180
cactagacat	ctcatcagcc	acttgtgtga	agagatgccc	catgaccccc	gatgcctctc	240
ccacccttac	ctccatctca	cacacttgag	cttccactc	tgtataattc	taacatcctg	300
gagaaaaatg	gcagtttgcac	caaacctgtt	cacaacggta	gaggctgatt	tctaacgaaa	360
ctttagaaat	gaacgcctgga					380

<210> 161		
<211> 114		
<212> DNA		
<213> Homo sapien		
<400> 161		
actccacatc ccctctgagc aggccgttgt cgttcaagggt gtatttgcc ttgcctgtca	60	
cactgtccac tggcccccta tccactttgt gcttaatccc tcgaaagagc atgt	114	
<210> 162		
<211> 177		
<212> DNA		
<213> Homo sapien		
<400> 162		
actttctgaa tcgaatcaaa tgatacttag ttagttta atatcctcat atatatcaaa	60	
gttttactac tctgataatt ttgtaaacca ggtaaccaga acatccagtc atacagcttt	120	
tggtgatata taacctggca ataacccagt ctggtgatac ataaaactac tcactgt	177	
<210> 163		
<211> 137		
<212> DNA		
<213> Homo sapien		
<220>		
<221> misc_feature		
<222> (1)...(137)		
<223> n = A,T,C or G		
<400> 163		
catttataaca gacaggcggt aagacattca cgacaaaaac gcgaaattct atcccggtac	60	
canagaaggc agctacggct actcctacat cctggcggtgg gtggccttcg cctgcacctt	120	
catcagcggc atgatgt	137	
<210> 164		
<211> 469		
<212> DNA		
<213> Homo sapien		
<220>		
<221> misc_feature		
<222> (1)...(469)		
<223> n = A,T,C or G		
<400> 164		
cttatacaca tgaatgttct cctgggcagc gttgtatct ttgccacctt cgtgacttta	60	
tgcaatgcat catgttattt catacctaat gagggagttc caggagattc aaccaggaaa	120	
tgcattggatc tcaaaggaaa caaacaccca ataaactcggtt gttggcagac tgacactgt	180	
gagacatgca cttgttacga aacagaaatt tcatgttgc cccctgttacacactgt	240	
ggttatgaca aagacaactg ccaaagaatc ttcaagaagg aggactgcaa gtatatcgtg	300	

gtggagaaga aggacccaaa aaagacctgt tctgtcagtg aatggataat ctaatgtgct	360
tctagtaggc acagggctcc caggccaggc ctcatctcc tctggctct aatagtcaat	420
gattgtgtag ccatgcctat cagaaaaag atnttgagc aaacacttt	469
<210> 165	
<211> 195	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1)...(195)	
<223> n = A,T,C or G	
<400> 165	
acagttttt atanatatcg acattgccgg cacttgtgtt cagttcata aagctgggg	60
atccgctgtc atccactatt ccttggctag agtaaaaatt attcttatacg cccatgtccc	120
tgcaggccgc ccgccccgtag ttctcggtcc agtcgtcttg gcacacaggg tgccaggact	180
tcctctgaga tgagt	195
<210> 166	
<211> 383	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1)...(383)	
<223> n = A,T,C or G	
<400> 166	
acatcttagt agtgtggcac atcagggggc catcagggtc acagtcactc atagcctcgc	60
cgaggtcgga gtccacaccca ccgggtgttagg tgtgtcaat cttgggttt ggcggccacct	120
ttggagaagg gatatgtgc acacacatgt ccacaaagcc tgtgaactcg ccaaagaatt	180
tttgcagacc agcctgagca aggggcggat gttcagcttc agtcctcct tcgtcaggtg	240
gatgccaacc tcgtctangg tccgtggaa gctgggtgtcc acntcaccta caacctgggc	300
gangatctta taaagaggct ccnagataaa ctccacgaaa cttctctggg agctgctagt	360
nggggccttt ttggtaact ttc	383
<210> 167	
<211> 247	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1)...(247)	
<223> n = A,T,C or G	
<400> 167	
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tggagcagaa actggagcaa gaagtgggcc tggggctgaa gtagagacca aggccactgc	120
tatanccata cacagagcca actctcaggc caaggcnatg gttggggcag anccagagac	180
tcaatctgan tccaaagtgg tggctggAAC actggcatg acanaggcag tgactctgac	240
tgangtc	247
<210> 168	
<211> 273	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1)...(273)	
<223> n = A,T,C or G	
<400> 168	
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aatccctcan ccttgttctt cacnactgtc tatactgana gtgtcatgtt tccacaaagg	120
gctgacacct gagcctgnat tttcactcat ccctgagaag ccctttccag tagggtggc	180
aattcccaac ttccctgcca caagcttccc aggcttctc ccctggaaaa ctccagcttg	240
agtcccagat acactcatgg gctgccctgg gca	273
<210> 169	
<211> 431	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1)...(431)	
<223> n = A,T,C or G	
<400> 169	
acagccttgg cttccccaaa ctccacagtc tcagtgcaga aagatcatct tccagcagtc	60
agctcagacc agggtcaaag gatgtgacat caacagtttc tggttcaga acaggttcta	120
ctactgtcaa atgacccccc atacttcctc aaaggctgtg gtaagtttg cacaggtgag	180
ggcagcagaa aggggtant tactgtatgg caccatctc tctgtatact ccacactgac	240
cttgccatgg gcaaaggccc ctaccacaaa aacaatagga tcactgctgg gcaccagctc	300
acgcacatca ctgacaaccg ggatggaaaa agaantgcc aacttcatac atccaaactgg	360
aaagtgtatct gatactggat tcttaattac cttaaaaagc ttctggggc catcagctgc	420
tcgaacactg a	431
<210> 170	
<211> 266	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1)...(266)	
<223> n = A,T,C or G	

<400> 170		
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tcaaggagct ctgcaggcat tttgc当地 ctctccanag canagggagc aacctacact		120
ccccgctaga aagacaccag attggagtcc tgggaggggg agttgggtg ggcatttgat		180
gtatacttgt cacctgaatg aangagccag agaggaanga gacgaanatg anattggcct		240
tcaaagctag gggctggca ggtgga		266
<210> 171		
<211> 1248		
<212> DNA		
<213> Homo sapien		
<220>		
<221> misc_feature		
<222> (1)...(1248)		
<223> n = A,T,C or G		
<400> 171		
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ctggtcatgg aaaacgaatt gttctgtcg ggcgtcctgg tgcatccgca gtgggtgctg		120
tcagccgac actgtttcca gaagttagt cagagctct acaccatcg gctgggcctg		180
cacagtctt aggccgacca agagccaggg agccagatgg tggaggccag cctctccgt		240
cgccacccag agtacaacag acccttgc gctaaccgacc tcatgctcat caagttggac		300
gaatccgtgt ccgagtctga caccatccgg agcatcagca ttgcttcgca gtgccttacc		360
gcgggaaact cttgcctcg ttctggctgg gtctgtctgg cgaacggcag aatgcctacc		420
gtgctgcagt gcgtgaacgt gtcgggtgt tctgaggagg tctgcagtaa gctctatgac		480
ccgctgtacc accccagcat gttctgc ggcggaggc aagaccagaa ggactcctgc		540
aacgggtact ctggggggcc cctgatctgc aacgggtact tgcagggcct tgcgtcttcc		600
ggaaaagccc cgtgtggcca agttggctg ccaggtgtct acaccaacct ctgcaaattc		660
actgagtgga tagaaaaac cgtccaggcc agttaactct ggggactggg aacccatgaa		720
attgacccccc aaatacatcc tgcggaagga attcaggaat atctgttccc agcccttcc		780
ccctcaggcc caggagtcca ggcggcc cctccctccc tcaaaccagg ggtacagatc		840
cccaagccct cctccctcg acccaggagt ccagacccccc cagccctcc tccctcagac		900
ccaggagtc accccctcct ccctcaggacc caggagtcca gaccccccag ccctccctcc		960
ctcagaccca ggggtccagg ccccaaccc ctccctccctc agactcagag gtccaagccc		1020
ccaaacccntc attccccaga cccagaggtc cagttccctc cccctcncc ctcagaccca		1080
gcggccaat gccacctaga ctntccctgt acacagtgcc cccttgc acgttgaccc		1140
aaccttacca gttggtttt cattttngt cccttcccc tagatccaga aataaaagttt		1200
aagagaagng caaa		1248
<210> 172		
<211> 159		
<212> PRT		
<213> Homo sapien		
<220>		
<221> VARIANT		
<222> (1)...(159)		
<223> Xaa = Any Amino Acid		

<400> 172
 Met Val Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Pro
 1 5 10 15
 Leu Leu Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser
 20 25 30
 Glu Ser Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr
 35 40 45
 Ala Gly Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly
 50 55 60
 Arg Met Pro Thr Val Leu Gln Cys Val Asn Val Ser Val Val Ser Glu
 65 70 75 80
 Glu Val Cys Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe
 85 90 95
 Cys Ala Gly Gly Gln Xaa Gln Xaa Asp Ser Cys Asn Gly Asp Ser
 100 105 110
 Gly Gly Pro Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe
 115 120 125
 Gly Lys Ala Pro Cys Gly Gln Val Gly Val Pro Gly Val Tyr Thr Asn
 130 135 140
 Leu Cys Lys Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Ala Ser
 145 150 155

<210> 173
<211> 1265
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(1265)
<223> n = A,T,C or G

<400> 173
ggcagccgc actcgacgca ctggcaggcg gcactggtca tggaaaacga attgttctgc 60
tcggcgatcc tggtgcatcc gcagtgggtg ctgtcagccg cacactgttt ccagaactcc 120
tacaccatcg ggctgggcct gcacagtctt gaggccgacc aagagccagg gagccagatg 180
gtggaggcca gcctctccgt acggcacca gagtacaaca gacccttgct cgctaacgac 240
ctcatgctca tcaagttgga cgaatccgtg tccagatctg acaccatccg gagcatcagc 300
attgcttcgc agtgcctac cgcggggaaac tcttgctctg tttctggctg gggctgtctg 360
gcgaacggtg agtcacggg tgggtgtctg ccctcttcaa ggaggtctc tgcccagtctg 420
cgggggctga cccagagctc tgctccag gcagaatgcc taccgtctg cagtgcgtga 480
acgtgtcggt ggtgtctgag gaggtctgca gtaagctcta tgaccgcgtg taccacccca 540
gcatgttctg cgcggcgga gggcaagacc agaaggactc ctgcaacgggt gactctgggg 600
ggccctgtat ctgcaacggg tacttgcagg gccttgcgtc ttctggaaaa gccccgtgtg 660
gccaagttgg cgtgccaggt gtctacacca acctctgcaa attcaactgag tggatagaga 720
aaaccgtcca ggccagttaa ctctggggac tggaaaccca tgaaattgac ccccaaatac 780
atcctgcgga aggaattcag gaatatctgt tcccagccccc tcctccctca ggcccgaggag 840
tccaggcccc cagccccctcc tccctcaaac caagggtaca gatccccagc ccctccccc 900
tcagacccag gagtccagac ccccccagccc ctccctccctc agacccagga gtccagcccc 960
tcctccntca gacccaggag tccagaccccc ccagccccctc ctccctcaga cccaggggtt 1020
gaggccccca acccctccctc cttcagagtc agaggtccaa gcccccaacc cctcgttccc 1080

cagacccaga ggttnnaggc ccagcccctc ttccntcaga cccagnggtc caatgccacc	1140
tagattttcc ctgnacacag tgcccccttg tggangttt acccaacctt accagttgg	1200
ttttcatttt tngtccctt cccctagatc cagaaataaa gtttaagaga nngcaaaaa	1260
aaaaaa	1265

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<210> 174
<211> 1459
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(1459)
<223> n = A,T,C or G

```

<400> 174	
ggtcagccgc acactgtttc cagaagttag tgcatagctc ctacaccatc gggctggcc	60
tgcacagtct tgaggccgac caagagccag ggagccagat ggtggaggcc agcctctccg	120
tacggcaccc agagtacaac agacccttgc tcgctaacga cctcatgctc atcaagttgg	180
acgaatccgt gtcccgagtct gacaccatcc ggagcatcag cattgcttcg cagtgcctta	240
ccgcggggaa ctcttcgcctc gtttctgtct ggggtctgtct ggccaacggt gagctcacgg	300
gtgtgtgtct gccctcttca aggaggctt ctgcccagtc gcgggggctg acccagagct	360
ctgcgtccca ggcagaatgc ctaccgtgt gcagtgcgtg aacgtgtcgg tgggtgtctga	420
ngaggtctgc antaagctct atgaccgcgt gtaccacccc ancatgttct ggcgcggcgg	480
agggcaagac cagaaggact cctgcaacgt gagagagggg aaagggggagg gcaggcgact	540
cagggaaaggg tggagaaggg ggagacagag acacacaggg ccgcattggcg agatgcagag	600
atggagagac acacagggag acagtgcacaa ctagagagag aaactgagag aaacagagaa	660
ataaacacag gaataaaagag aagcaaagga agagagaaac agaaacacagac atggggaggc	720
agaaacacac acacatagaa atgcagtgtc ctttccaaca gcatggggcc tgagggcggt	780
gacctccacc caatagaaaa ttctttata acttttact ccccaaaaac ctgactagaa	840
atgcctact gttgacgggg agccttacca ataaacataaa tagtcgattt atgcatacgt	900
tttatgcatt catgatatac ctttggat attttttgtat atttctaaac tacacagttc	960
gtctgtgaat tttttttaaat ttttgcaact ctccctaaat ttttctgtat tgtttattga	1020
aaaaatccaa gtataagtgg acttggcat tcaaaccagg gttgttcaag ggtcaactgt	1080
gtacccagag ggaaacagtg acacagattc atagaggtga aacacgaaga gaaacaggaa	1140
aatcaagac tctacaaaga ggctggcag ggtggctcat gcctgtatc ccagcacttt	1200
gggaggcggag gcaggcagat cacttgaggt aaggagttca agaccgcct ggccaaaaatg	1260
gtgaaatct gtctgtacta aaaataaaaa agtttagctgg atatggtggc aggccctgt	1320
aatcccagct acttgggagg ctgaggcagg agaattgctt gaatatggga ggcagaggtt	1380
gaagtgagtt gagatcacac cactatactc cagctgggc aacagagtaa gactctgtct	1440
aaaaaaaaaaaa aaaaaaaaaaa	1459

```

<210> 175
<211> 1167
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(1167)
<223> n = A,T,C or G

```

<400> 175

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gcmcagccct ggcaggcggc actggtcatg gaaaacgaat tttctgtc gggcgccctg      60
gtgcatccgc agtgggtgct gtcagccgca cactgttcc agaactccta caccatcgaa    120
ctgggcctgc acagtcttga ggccgaccaa gagccaggaa gccagatggt ggaggccagc    180
ctctccgtac ggcacccaga gtacaacaga ctcttgcgtc ctaacgacct catgctcatc    240
aagttggacg aatccgtgtc cgagtctgac accatccgaa gcatcagcat tgcttcgcag    300
tgccctaccg cggggaaactc ttgcctcgtn tctggctggg gtctgctggc gaacggcaga    360
atgcctaccg tgctgcactg cgtgaacgtc tcgggtgtgt ctgaggangt ctgcagtaag    420
ctctatgacc cgctgtacca ccccaacatg ttctgcgcgc gcggaggcga agaccagaag    480
gactcctgca acggtgactc tggggggccc ctgatctgca acgggtactt gcagggcctt    540
gtgtcttcg gaaaagcccc gtgtggccaa cttggcgtgc caggtgtcta caccAACCTC    600
tgcaattca ctgagtgat agagaaaacc gtccagncca gttaactctg gggactggg      660
accatgaaa ttgacccca aatacatctt gccaangaa ttcaagaaata tctgttccca    720
gccctccctc cctcaggccc aggagtccag gccccccagcc cctcctccct caaaccaagg    780
gtacagatcc ccagccctc ctccctcaga cccaggagtc cagaccccccc agccctcnt    840
ccntcagacc caggagtcca gcccctctc cntcagacgc aggagtccag accccccccgc    900
ccntcncctc tcagacccag gggtgtcaggc ccccaacccc tcntcncntca gagtcagagg    960
tccaagcccc caacccctcg ttccccagac ccagaggtnc aggtcccagc ccctcctccc   1020
tcagacccag cggtccaatg ccacctagan tntccctgta cacagtgccc cttgtggca   1080
ngttgaccca accttaccag ttggttttc atttttgtc cttttccct agatccagaa   1140
ataaaagtna agagaagcgc aaaaaaaaaa                                1167

```

<210> 176

<211> 205

<212> PRT

<213> Homo sapien

<220>

<221> VARIANT

<222> (1)...(205)

<223> Xaa = Any Amino Acid

<400> 176

Met	Glu	Asn	Glu	Leu	Phe	Cys	Ser	Gly	Val	Leu	Val	His	Pro	Gln	Trp
1									10					15	
Val	Leu	Ser	Ala	Ala	His	Cys	Phe	Gln	Asn	Ser	Tyr	Thr	Ile	Gly	Leu
									20					25	
Gly	Leu	His	Ser	Leu	Glu	Ala	Asp	Gln	Glu	Pro	Gly	Ser	Gln	Met	Val
									35					40	
Glu	Ala	Ser	Leu	Ser	Val	Arg	His	Pro	Glu	Tyr	Asn	Arg	Leu	Leu	
									50					55	
Ala	Asn	Asp	Leu	Met	Leu	Ile	Lys	Leu	Asp	Glu	Ser	Val	Ser	Glu	Ser
									65					70	
Asp	Thr	Ile	Arg	Ser	Ile	Ser	Ile	Ala	Ser	Gln	Cys	Pro	Thr	Ala	Gly
									85					90	
Asn	Ser	Cys	Leu	Val	Ser	Gly	Trp	Gly	Leu	Leu	Ala	Asn	Gly	Arg	Met
									100					105	
Pro	Thr	Val	Leu	His	Cys	Val	Asn	Val	Ser	Val	Val	Ser	Glu	Xaa	Val
									115					120	
Cys	Ser	Lys	Leu	Tyr	Asp	Pro	Leu	Tyr	His	Pro	Ser	Met	Phe	Cys	Ala

130	135	140
Gly	Gly	Gly
Gly	Gly	Gln
Gly	Gly	Asp
Gln	Gly	Gln
Lys	Asp	Ser
Asn	Ser	Cys
Cys	Asn	Asn
Asn	Gly	Gly
Gly	Tyr	Asp
Leu	Leu	Ser
Ile	Gln	Gly
Cys	Gly	Gly
Pro	Leu	Asp
Leu	Ile	Ser
Ile	Cys	Gly
Cys	Asn	Gly
Ala	Pro	Gly
Pro	Cys	Gly
Gly	Gln	Gly
Gln	Leu	Val
Leu	Gly	Pro
Gly	Tyr	Gly
Val	Leu	Val
Pro	Gly	Tyr
Gly	Val	Thr
Val	Tyr	Asn
Tyr	Thr	Leu
Asn	Asn	Cys
Lys	Phe	Phe
Phe	Thr	Trp
Thr	Glu	Ile
Glu	Lys	Glu
Lys	Thr	Val
Thr	Val	Gln
Val	Gln	Xaa
Gln	Xaa	Ser

195	200	205
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<210> 177

<211> 1119

<212> DNA

<213> Homo sapien

<400> 177

gcmcactcgc	agccctggca	ggcgccactg	gtcatggaaa	acgaattgtt	ctgctcgccc	60
gtcctgggtgc	atccgcagtgc	ggtgctgtca	gcccacact	gtttccagaa	ctcctacacc	120
atcgggctgg	gcctgcacag	tcttgaggcc	gaccaagagc	cagggagcca	gatgggtggag	180
gccagcctct	ccgtacggca	cccagagta	aacagaccct	tgctcgctaa	cgacacctatg	240
ctcatcaagt	tggacgaatc	cgtgtccag	tctgacacca	tccggagcat	cagcattgct	300
tcgcagtgcc	ctaccgcggg	gaactcttc	ctcgttctg	gctgggtct	gctggcgaac	360
gatgctgtga	ttgccccatcca	gtcccagact	gtgggaggct	gggaggtgtga	gaagcttcc	420
caaccctggc	agggttgtac	catttcggca	acttccagtg	caaggacgta	ctgctgcata	480
ctcaactgggt	gctcaactact	gctcaactgca	tcacccggaa	cactgtgatc	aactagccag	540
caccatagtt	ctccgaagtc	agactatcat	gattactgtg	ttgactgtgc	tgtctattgt	600
actaaccatg	ccgatgttta	ggtgaaatta	gctgacttg	gcctcaacca	tcttggtata	660
cagtttatcct	cactgaattt	agatttcctg	cttcactgtc	agccattccc	acataatttc	720
tgacctacag	aggtgaggga	tcatatagt	cttcaaggat	gctggtaactc	ccctcacaaa	780
ttcatttttc	ctgttgttagt	gaaaggtgcg	ccctctggag	cctcccagg	tgggtgtgca	840
ggtcacaatg	atgaatgtat	gatcgtgttc	ccattaccca	aagcctttaa	atccctcatg	900
ctcagtagcac	caggcaggt	ctagcatttc	ttcatttagt	gtatgctgtc	cattcatgca	960
accacctcag	gactcctgga	ttctctgcct	agttgagctc	ctgcatgctg	cctccttggg	1020
gaggtgaggg	agagggccca	tggttcaatg	ggatctgtc	agttgtaaaca	cattaggtgc	1080
ttaataaaaca	gaagctgtga	tgttaaaaaaa	aaaaaaaaaa			1119

<210> 178

<211> 164

<212> PRT

<213> Homo sapien

<220>

<221> VARIANT

<222> (1)...(164)

<223> Xaa = Any Amino Acid

<400> 178

Met	Glu	Asn	Glu	Leu	Phe	Cys	Ser	Gly	Val	Leu	Val	His	Pro	Gln	Trp
1				5					10				15		
Val	Leu	Ser	Ala	Ala	His	Cys	Phe	Gln	Asn	Ser	Tyr	Thr	Ile	Gly	Leu
									20				25		30

Gly Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met Val
 35 40 45
 Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Pro Leu Leu
 50 55 60
 Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu Ser
 65 70 75 80
 Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala Gly
 85 90 95
 Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Asp Ala Val
 100 105 110
 Ile Ala Ile Gln Ser Xaa Thr Val Gly Gly Trp Glu Cys Glu Lys Leu
 115 120 125
 Ser Gln Pro Trp Gln Gly Cys Thr Ile Ser Ala Thr Ser Ser Ala Arg
 130 135 140
 Thr Ser Cys Cys Ile Leu Thr Gly Cys Ser Leu Leu Leu Thr Ala Ser
 145 150 155 160
 Pro Gly Thr Leu

<210> 179		
<211> 250		
<212> DNA		
<213> Homo sapien		
<400> 179		
ctggagtgcc ttgggtttc aagccctgc aggaaggaga atgcacccatc tgaggcacct	60	
ccagctgccc ccggccgggg gatgcgaggc tcggagcacc cttggccggc tgtgattgct	120	
gccaggcaact gttcatctca gcttttctgt ccctttgctc ccggcaagcg ctctgctga	180	
aagttcatat ctggagccctg atgtcttaac gaataaaggc cccatgctcc acccgaaaaaa	240	
aaaaaaaaaaa	250	
<210> 180		
<211> 202		
<212> DNA		
<213> Homo sapien		
<400> 180		
actagtccag tgggtggaa ttccattgtt ttggggccaa cacaatggct acctttaaca	60	
tcacccagac cccgccccctg cccgtgcccc acgctgctgc taacgacagt atgatgctta	120	
ctctgctact cgaaaaactat ttttatgtaa ttaatgtatg ctttcttgaa tataaatgcc	180	
tgatttaaaa aaaaaaaaaaa aa	202	
<210> 181		
<211> 558		
<212> DNA		
<213> Homo sapien		
<220>		
<221> misc_feature		
<222> (1)...(558)		
<223> n = A,T,C or G		

<400> 181	
tccytttgkt naggttkkg agacamccc agacctaann ctgtgtcaca gacttcyngg	60
aatgtttagg cagtgcgt aatttcytcg taatgattct gttattactt tcctnattct	120
ttattccctt ttcttctgaa gattaatggaa gttgaaaatt gaggtggata aataaaaaaa	180
ggtagtgtga tagtataagt atctaagtgc agatgaaagt gtgttatata tatccattca	240
aaattatgca agttagtaat tactcagggta taactaaatt actttaatat gctgttgaac	300
ctactctgtt ccttggctag aaaaaattaa aacaggact ttgttagttt gggaaagccaa	360
attgataata ttctatgttc taaaagtgg gctatacata aattattaag aaatatggaw	420
ttttattccc aggaatatgg kgttcatttt atgaatatta cscrggatag awgtwtgagt	480
aaaaycagtt ttggtaata ygtwaatatg tcmtaaataa acaakgctt gacttatttc	540
aaaaaaaaaaaaaaa aaaaaaaaaaaaaaaa	558
<210> 182	
<211> 479	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1)...(479)	
<223> n = A,T,C or G	
<400> 182	
acagggwtk grggatgcta agscccrga rwtygtttga tccaaaccctg gcttwtttc	60
agaggggaaa atggggccta gaagttacag mscatyttagy tggtgcgmgt gcacccctgg	120
cstcacacag astcccgagt agctggact acaggcacac agtcactgaa gcaggccctg	180
ttwgcaattc acgttgccac ctccaactta aacattcttc atatgtgatg tccttagtca	240
ctaaggttaa actttccac ccagaaaagg caacttagat aaaatcttag agtactttca	300
tactmttcta agtctcttc cagcctcaact kkgagtccctm cytgggggtt gataggaant	360
ntctcttggc tttctcaata aartctctat ycactctatg tttatattgg tacgcatara	420
awtgstgara aaattaaaat gttctggty mactttaaaa araaaaaaa aaaaaaaaa	479
<210> 183	
<211> 384	
<212> DNA	
<213> Homo sapien	
<400> 183	
aggcgggagc agaagctaaa gccaaagccc aagaagagtgcagactggtgcc	60
agtaccagta ccaataacag tgccagtgcc agtgcgcagca ccagtgggtt cttcagtgt	120
ggtgccagcc tgaccgccc tctcacattt gggcttctcg ctggccttgg tggagctgg	180
gccagcacca gtggcagctc tggtgcctgt ggttctctt acaagtgaga ttttagat	240
tgttaatctt gccagtctt ctcttcaagc cagggtgcat cctcagaaac ctactcaaca	300
cagcactcta ggcagccact atcaatcaat tgaagttgac actctgcatt aratctattt	360
gccatttcaa aaaaaaaaaaaaaaaa aaaa	384
<210> 184	
<211> 496	
<212> DNA	
<213> Homo sapien	

<220>
 <221> misc_feature
 <222> (1)...(496)
 <223> n = A,T,C or G

<400> 184

accgaattgg	gaccgctggc	ttataagcga	tcatgttynt	ccrgtatkac	ctcaacgagc	60
agggagatcg	agtctatacg	ctgaagaaat	ttgaccgcgt	gggacaacag	acctgctcag	120
cccatcctgc	tcggttctcc	ccagatgaca	aatactctsg	acaccgaatc	accatcaaga	180
aacgcttcaa	ggtgctcatg	acccagcaac	cgcgcctgt	cctctgaggg	tcccttaaac	240
tgatgtctt	tctgccacct	gttaccctc	ggagactccg	taaccaaact	cttcggactg	300
tgagccctga	tgccttttg	ccagccatac	tcttggcat	ccagtctctc	gtggcgattg	360
attatgcttg	tgtgaggcaa	tcatggtggc	atcacccata	aaggaaacac	atttgacttt	420
ttttctcat	attttaaatt	actacmagaw	tattwmagaw	waaatgawtt	gaaaaactst	480
aaaaaaaaaa	aaaaaaa					496

<210> 185
 <211> 384
 <212> DNA
 <213> Homo sapien

<400> 185

gctggtagcc	tatggcgkgg	cccacggagg	ggctcctgag	gccacggrac	agtgacttcc	60
caagtatcyt	gchgcsccgtc	ttctaccgtc	cctacctgca	gatcttcggg	cagattcccc	120
aggaggacat	ggacgtggcc	ctcatggagc	acagcaactg	ytcgctggag	cccggtttct	180
gggcacaccc	tcctggggcc	caggcggca	cctgcgtctc	ccagtatgcc	aactggctgg	240
tggtgctgct	cctcgtcatac	ttcctgctcg	tggccaacat	cctgctggtc	aacttgctca	300
ttgccatgtt	cagttacaca	ttcggcaaag	tacagggcaa	cagcgatctc	tactggaaag	360
gcgcagcggtt	accgcctcat	ccgg				384

<210> 186
 <211> 577
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(577)
 <223> n = A,T,C or G

<400> 186

gagtttagctc	ctccacaacc	ttgatgaggt	cgtctgcagt	ggcctctcg	ttcataccgc	60
tnccatcg	tc atactgtagg	tttgccacca	cytccctggca	tcttggggcg	gcntaatatt	120
ccagggaaact	ctcaatcaag	tcaccgtcg	tgaaacctgt	gggctggttc	tgtctccgc	180
tcggtgtgaa	aggatctccc	agaaggagt	ctcgatctc	cccacacttt	tgtacttt	240
attgagtctcg	ttctgcatgt	ccagcaggag	gtttagccag	ctctctgaca	gtgaggtcac	300
cagccctatc	atgcgttga	mcgtggcaa	garccaggag	ccttgggtgg	gggkkgaaagt	360
ctcacccaga	ttctgcatta	ccagagagcc	gtggcaaaag	acattgacaa	actcgcccag	420
gtggaaaaaaag	amcamctct	ggargtgc	gccctctc	gtcmgttgg	ggcagcgtw	480
tcctttgac	acacaaacaa	gtttaaggca	tttcagccc	ccagaaantt	gtcatcatcc	540

aagatntcgc acagcactna tccagttggg attaaat	577
<210> 187	
<211> 534	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1)...(534)	
<223> n = A,T,C or G	
<400> 187	
aacatcttcc tgtataatgc tgtgttaatat cgatccgatn ttgtctgstg agaatycatw	60
actkggaaaa gmaacattaa agcctggaca ctgttattaa aattcacaat atgcaacact	120
ttaaacagtg tgtcaatctg ctcccyymac tttgtcatca ccagtctggg aakaaggta	180
tgccttattc acacctgtta aaagggcgct aagcatttt gattcaacat ctttttttt	240
gacacaagtc cgaaaaaaagc aaaagtaaac agttatyaat ttgttagcca attcactttc	300
ttcatgggac agagccatyt gattaaaaaa gcaaattgca taatatttag ctttygggagc	360
tgatatttga gcggaagagt agcctttcta cttcaccaga cacaactccc tttcatattg	420
ggatgttnac naaagtwtg tctcttwacag atggatgct tttgtggcaa ttctgttctg	480
aggatctccc agtttattta ccacttgcac aagaaggcgt tttcttcctc aggc	534
<210> 188	
<211> 761	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1)...(761)	
<223> n = A,T,C or G	
<400> 188	
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cctcttttgt atctatatct gtgaaagttt taatgatctg ccataatgtc ttggggacct	180
ttgtcttctg tgtaaatggt actagagaaa acacctatnt tatgagtcaa tctagttngt	240
tttattcgtac atgaaggaaa ttccagatn acaacactna caaactctcc ctkgackarg	300
ggggacaagaaa aaaagcaaaa ctgamctaa raaacaatwa cctggtgaga arttgataa	360
acagaaatwr ggtagttat tgaarnacag catcattaaa rmgttwtktt wttctccctt	420
gcaaaaaaaca tgcacngact tcccgttgag taatgccaag ttgtttttt tatnataaaa	480
cttgccttc attacatgtt tnnaaagtggt gtggtgggcc aaaatattga aatgatggaa	540
ctgactgata aagctgtaca aataagcagt gtgcctaaca agcaacacag taatgttgac	600
atgcttaatt cacaatgtct aatttcattt aataatgtttg ctaaaataca ctttgaacta	660
tttttctgtt tccctcagac tgagatntt gattttatgt agtatnaagt gaaaaantac	720
gaaaataata acattgaaga aaaananaaa aaanaaaaaaaaa a	761
<210> 189	
<211> 482	
<212> DNA	

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(482)

<223> n = A,T,C or G

<400> 189

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caccggggct atnagaagca agaaggaagg agggagggca cagcccttg ctgagcaaca	120
aagccgcctg ctgccttctc tgtctgtctc ctggcgcagg cacatggga gaccttcccc	180
aaggcagggg ccaccagtcc aggggtggga atacaggggg tgggangtgt gcataagaag	240
tgataggcac aggcccacccg gtacagaccc ctccgctctc gacaggtnga tttcgaccag	300
gtcattgtgc cctgcccagg cacagcgtan atctggaaaa gacagaatgc tttcctttc	360
aaatttgct ngtcatngaa ngggcanttt tccaanttng gctnggtctt ggtacncttg	420
gttcggccca gctccncgtc caaaaantat tcacccnnct ccnaattgct tgcnngnccc	480
cc	482

<210> 190

<211> 471

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(471)

<223> n = A,T,C or G

<400> 190

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aaaactctcg catccagtga gaactaccat acaccacatt acagctngga atgtntccca	120
aatgtctggt caaatgatac aatggAACCA ttcaatctta cacatgcacg aaagaacaag	180
cgctttgac atacaatgca caaaaaaaaaa aggggggggg gaccacatgg attaaaaattt	240
taagtactca tcacatacat taagacacag ttctagtcctt gtcnaaaatc agaactgcnt	300
tgaaaaattt catgtatgca atccaaccaa agaacttnat tggtgatcat gantnctcta	360
ctacatcnac cttgtatcatt gccaggaacn aaaagttcaa ancacnctgt acaaaaanaa	420
tctgtattn anttcaacct ccgtacngaa aaatntnnnt tatacactcc c	471

<210> 191

<211> 402

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(402)

<223> n = A,T,C or G

<400> 191

gagggattga aggtctgttc tastgtcggm ctgttcagcc accaactcta acaagttgct	60
gtcttccact cactgtctgt aagctttta acccagacwg tatcttcata aatagaacaa	120

attcttcacc agtcacatct tctaggacct ttttggattc agttagtata agctttcca	180
cttccttgt taagacttca tctggtaaaag tcttaagtt tgttagaaagg aattyaaattg	240
ctcggtctct aacaatgtcc tctccttcaa gtatggct gaacaaccca cctaaagtcc	300
ctttgtgcat ccatttaaa tatacttaat agggcattgk tncacttaggt taaattctgc	360
aagagtcatc tgtctgcaaa agttgcgtt gtatatctgc ca	402
<210> 192	
<211> 601	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1)...(601)	
<223> n = A,T,C or G	
<400> 192	
gagctcggat ccaataatct ttgtctgagg gcagcacaca tatncagtgc catggnaact	60
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atgcyyttt gaytaccgtg tgccaagtgc tggtgattct yaacacacyt ccatcccggt	180
ctttgtgga aaaactggca ctktcttga actagcarga catcaattac aaattcaccc	240
acgagacact taaaagggtt aacaaagcga ytcttgcatt gcttttgtc cctccggcac	300
cagttgtcaa tactaacccg ctggtttgc tccatcacat ttgtgatctg tagctctgga	360
tacatctcct gacagtactg aagaacttct tctttgttt caaaagcerc tcttgggtcc	420
tgttggatca ggttcccatt tcccagtcyg aatttcaca tggcatattt wacttcccac	480
aaaacattgc gatttgaggc tcagcaacag caaatcctgt tccggcattt gctgcaagag	540
cctcgatgtc gccggccagc gccaaggcag gcggcgttag cccaccaggc agcagaagca	600
g	601
<210> 193	
<211> 608	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1)...(608)	
<223> n = A,T,C or G	
<400> 193	
atacagccca natccacca cgaagatgcg ctgttgact gagaacctga tgcggtaact	60
ggtcccgctg tagccccagc gactctccac ctgctggaaag cggttgcgtc tgactcytt	120
cccaacgcag gcagmagcgg gsccggtaaa tgaactccay tcgtggctt gggtkgacgg	180
tkaagtgcag gaagaggctg accacctcgc ggtccaccag gatgcccac tgcggggac	240
ctgcagcga actcctcgat ggtcatgagc gggaaagcga tgaggcccag ggccttgc	300
agaaccttcc gcctgttctc tggcgtcacc tgcagctgtt gccgctgaca ctccgcctcg	360
gaccagcggc caaacggcrt tgaacagccg cacctcacgg atgcccagtg tgcgcgtc	420
caggammgsc accacgcgtt ccaggtcaat gtccgtgaag ccctccgcgg gtratggcgt	480
ctgcagtgtt ttgtcgatg ttctccaggc acaggctggc cagctgcgtt tcatcgaaga	540
gtcgccgtc cgtgagcgc atgaaggcgt tgcggctcg cagttttct tcaggaactc	600
cacgcaat	608

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<210> 194
<211> 392
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(392)
<223> n = A,T,C or G

<400> 194
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ccagtccag cagccccaga ccgctgccgc ccgaagctaa gcctgcctct ggccccc       120
tccgcctcaa tgcagaaccca gtagtgggag cactgtgttt agagttaaaa gtgaacactg     180
tttgattttt ctgggaatt tcctctgtta tatacgcttt cccaatgcta atttccaaac     240
aacaacaaca aaataaacatg ttgcctgtt aagttgtata aaagtaggtg attctgtatt   300
taaagaaaaat attactgtta catatactgc ttgcaatttc tgtattttt gktnctstgg    360
aaataaaatat agttattaaa ggttgtcant cc                                392

<210> 195
<211> 502
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(502)
<223> n = A,T,C or G

<400> 195
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ccgagcttag gcagatgttc ccacagtgcac cccagagcc stgggstatata gtytctgacc 120
cctcncaagg aaagaccacs ttctgggac atgggcttggaa gggcaggacc tagaggcacc 180
aaggaaaggc cccattccgg ggstgttccc cgaggaggaa gggaaaggccc tctgtgtgcc 240
ccccasgagg aagaggccct gagtccttggg atcagacacc cttcacgtg tatccccaca 300
caaatgcaag ctcaccaagg tcccctctca gtccccttcc stacaccctg amcggccact 360
gscscacacc cacccagagc acgccacccg ccatggggar tgtgctcaag gartcgcnng 420
gcarcgtgga catctngtcc cagaaggggg cagaatctcc aatagangga ctgarcmstt 480
gctnanaaaa aaaaanaaaaa aa                                502

<210> 196
<211> 665
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(665)
<223> n = A,T,C or G

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<400> 196	
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wagctgttk gagttgatts gcaccactgc accacaact tcaatatgaa aacyawttga	180
actwatttat tatcttgta aaagtataac aatgaaaatt ttgttcatac tgtattkato	240
aagtatgatg aaaagcaawa gatatatatt ctittattat gttaaattat gattgccatt	300
attaatccgc aaaatgtgga gtgtatgtt tttcacagt aatatatgcc ttttgtaact	360
tcacttgggtt attttattgt aaatgarrrt caaaattctt aatthaagar aatggtatgt	420
watatttatt tcattaattt ctccctkgt ttacgtwaat ttgaaaaaga wtgcatgatt	480
tcttgacaga aatcgatctt gatgctgtgg aagtagttt acccacatcc ctatgagttt	540
ttctttagaat gtataaaggt ttagccccat cnaacttcaa agaaaaaaaaat gaccacatac	600
tttgcataatca ggctgaaaatg tggcatgtn ttctaattcc aactttataa actagcaaan	660
aagtg	665
<210> 197	
<211> 492	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1)...(492)	
<223> n = A,T,C or G	
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atgtttattt gagcgatcca ttatcagtga aaagtatcaa gtgttataa natttttagg	120
aaggcagatt cacagaacat gctngtcngc ttgcagttt acctcgtana gatnacagag	180
aattatagtc naaccagttaa acnaggaatt tactttcaa aagattaaat ccaaactgaa	240
caaaattcta ccctgaaact tactccatcc aaatattgga ataanagtca gcagtgatac	300
attctcttct gaactttaga ttttctagaa aaatatgtaa tagtgatcag gaagagctct	360
tgttcaaaag tacaacnaag caatgttccc ttaccatagg ccttaattca aactttgatc	420
catttcactc ccatcacggg agtcaatgct acctgggaca cttgtatTTT gttcatnctg	480
ancntggctt aa	492
<210> 198	
<211> 478	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1)...(478)	
<223> n = A,T,C or G	
<400> 198	
tttnttttgn atttcantct gtannaanta ttttcattat gtttattana aaaatatnaa	60
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tgagtatatt ttgaaaagga caagttaaa gtanacncat attgccganc atancacatt	180
tatacatggc ttgattgata tttagcacag canaaaactga gtgagttacc agaaanaaat	240
natatatgtc aatcngattt aagataaaaa acagatccta tgg tacatan catcntgtag	300

gagttgtggc tttatgttta ctgaaagtca atgcagttcc tgtacaaaga gatggccgta	360
agcattctag tacctctact ccatggtaa gaatcgata cttatgttta catatgtncat	420
gggtaagaat tgtgttaagt naanttatgg agaggtccan gagaaaaatt tgatncaa	478
<210> 199	
<211> 482	
<212> DNA	
<213> Homo sapien	
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<221> misc_feature	
<222> (1)...(482)	
<223> n = A,T,C or G	
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tgctagttcc tgtcatctat tcgctactaa atgcagactg gaggggacca aaaaggggca	120
tcaactccag ctggattatt ttggagcctg caaatctatt cctacttgta cgactttga	180
agtgattcag tttctctac ggatgagaga ctgctcaag aatatcctca tgcagcttta	240
tgaagccnac tctgaacacg ctggttatct nagatgagaa ncagagaaaat aaagtcnaga	300
aaatttacct ggangaaaaag aggcttngg ctggggacca tcccattgaa ccttctctta	360
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ga	482
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<222> (1)...(270)	
<223> n = A,T,C or G	
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cgactgcgac gacggccgcg gcgacagtgc caggtgcagc gcgggcgcct ggggtcttgc	120
aaggctgagc tgacgcccga gaggtcggtt cacgtccccac gaccttgacg ccgtcggggaa	180
cagccggAAC agagccccgtt gaangcggga ggcctcgggg agcccctcgga gaagggcggc	240
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<211> 419	
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<222> (1)...(419)	
<223> n = A,T,C or G	

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aatctcttat gctatatcat attttaagt aaactaatga gtcactggct tatcttctcc	180
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cattacaaaa ctgctcaaat tgtttgtaa gnttatccat tataatttagt tnngcaggag	420
ctaatacaaaa tcacatttac ngacnagcaa taataaaaact gaagtaccag ttaaatatcc	480
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ttaagatcat agagcttgc agtgaaaaga taaaatttga cctcagaaac tctgagcatt	240
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aaccc	545
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<212> DNA	
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cccttctccc accaactaat gaancagcaa cattagttt attttattag tagatnatac	240	
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tcacaaaa	487	
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<211> 332		
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<221> misc_feature		
<222> (1) ... (332)		
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atctttgcat gcagaggagg taaaaggat tggatttca cagaggaana acacagcgca	240	
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<211> 524		
<212> DNA		
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tttaaaggac atggagcttgc tcacaatgtc acaatgtcac agtgtgaagg gcacactcac	180	
tcccgctgtca ttcacattta gcaaccaaca atagctcatg agtccatact tgtaataact	240	
tttggcagaa tactnttga aacttgcaga tgataactaa gatccaagat atttcccaa	300	
gtaaatagaa gtgggtcata atattaatata cctgttcaca tcagcttcca tttacaagtc	360	

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tggggagatt ttanccaatt tangtntgta aatggggaga ctggggcagg cgggagagat	180
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<223> n = A,T,C or G	
<400> 211	
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atattcaagc acatatgtta tatattattc agtccatgt ttatagccta gttaaggaga	180
ggggagatac attcngaaag aggactgaaa gaaatactca agtngaaaa cagaaaaaga	240
aaaaaaaggag caaatgagaa gcct	264
<210> 212	
<211> 328	
<212> DNA	

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(328)

<223> n = A,T,C or G

<400> 212

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ggatttaatg ttgtctcagc ttgggcactt cagtaggac ctaaggatgc cagccggcag	120
gttttatatat gcagcaacaa tattcaagcg cgacaacagg ttattgaact tgcccgcag	180
ttnaatttca ttcccattga ctgggatcc ttatcatcag ccagagagat tgaaaattta	240
ccccctacnac tcttactct ctgganaggg ccagtggtgg tagctataag ctggccaca	300
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<210> 213

<211> 250

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(250)

<223> n = A,T,C or G

<400> 213

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taaagcattt ctcactgaag ggatagaagt gactgccagg agggaaagta agccaaggct	120
cattatgcca aagganatat acatttcaat tctccaaact tcttcctcat tccaagagtt	180
ttcaatattt gcatgaacct gctgataanc catgttaana aacaaatatc tctctnacct	240
tctcatcggt	250

<210> 214

<211> 444

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(444)

<223> n = A,T,C or G

<400> 214

acccagaatc caatgctgaa tatttggctt cattattccc agattcttg attgtcaaag	60
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tttatatatg cagcaacaat attcaagcgc gacaacaggt tattgaactt gccgcgcagt	180
tgaatttcat tcccattgac ttgggatcct tatcatcago canagagatt gaaaatttac	240
ccctacgact cttaactctc tggagagggc cagtggtggt agctataagc ttggccacat	300
ttttttttcc tttattcctt tgtcagagat gcgattcatac catatgctan aaaccaacag	360
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actttgctct ccctaataata cctc	444

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<210> 215
<211> 366
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(366)
<223> n = A,T,C or G

<400> 215
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cattatgcca aagganatat acatttcaat tctccaaact tttccctcat tccaagagtt 180
ttcaatattt gcatgaacct gctgataagc catgttgaga aacaatatac tctctgacct 240
tctcatcggt aagcagaggc tgttaggaac atggaccata gcgaanaaaa aacttagtaa 300
tccaagctgt ttctacact gtaaccaggt ttccaaaccaa ggtggaaatc tcctataactt 360
gggcc 366

<210> 216
<211> 260
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(260)
<223> n = A,T,C or G

<400> 216
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caagacaggg gcctaaggag ggtctccaca ctgctnnntaa gggctnntnc atttttttat 120
taataaaaaag tnnaaaaaggc ctcttctcaa ctttttccc ttnggctgga aaatttaaaa 180
atcaaaaaatt tcctnaagtt ntcaagctat catataact ntatcctgaa aaagcaacat 240
aattcttcctt tccctccctt 260

<210> 217
<211> 262
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(262)
<223> n = A,T,C or G

<400> 217
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tcttgccat aattttctat ttataataagg aaatagcaaa ttgggggtggg ggaatgttag 120
qqcatttctac agtttgagca aaatgcaatt aaatgtggaa ggacagcact gaaaaatttt 180

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atgaataatc tgtatgatta tatgtctcta gagtagattt ataattagcc acttacccta	240
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<210> 218	
<211> 205	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1)...(205)	
<223> n = A,T,C or G	
<400> 218	
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ccccttatcaa ctccctttg tagtaaactt ggaaccttgg aaatgaccag gccaaagactc	120
aggcctcccc agttctactg acctttgtcc ttangtnna ngtccagggt tgcttaggaaa	180
anaaatcagc agacacaggt gtaaa	205
<210> 219	
<211> 114	
<212> DNA	
<213> Homo sapien	
<400> 219	
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accacgaagt tgatttctct tgtgtgcaga gtgactgatt ttaaaggaca tggaa	114
<210> 220	
<211> 93	
<212> DNA	
<213> Homo sapien	
<400> 220	
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aaataagcat ttagtgctca gtccctactg agt	93
<210> 221	
<211> 167	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1)...(167)	
<223> n = A,T,C or G	
<400> 221	
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tcttttgcggc agcctgtggc tctactgttag taagttctg ctgatgaggg gccagnatgc	120
ccccccactac ctccccctgac gctccccana aatcacccaa cctctgt	167

<210>	222						
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<212>	DNA						
<213>	Homo sapien						
<400>	222						
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atgtttgct	g	aattaaagga	tggataaaaa	aaattaataa	tgaattttg	cataatccaa	180
ttttctctt	tatatttcta	gaagaagttt	cttgagcct	attagatccc	ggaaatcttt	240	
taggtgagc	ta	tgattagaga	gcttgtaggt	tgctttaca	tatatctggc	atatttgagt	300
ctcgat	atcaa	aacaatagat	tggtaaagg	ggtattattt	tattgataag	t	351
<210>	223						
<211>	383						
<212>	DNA						
<213>	Homo sapien						
<220>							
<221>	misc_feature						
<222>	(1) ... (383)						
<223>	n = A,T,C or G						
<400>	223						
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ttaaaatgtc	tgtccaaaaa	ttttgttattt	tatttgaga	cttcttatca	aaagtaatgc	180	
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<212>	DNA						
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gagaaaatac	tacttctcr	aatggaaagc	ccttaaagg	gcttgatac	tgaaggacac	240	
aatgtggcc	gtccatcctc	cttaragtt	gcatgactt	gacacggtaa	ctgtgcagt	300	
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<212>	DNA						
<213>	Homo sapien						

<400> 225

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cagatggtgg	aggccagcct	ctccgtacgg	caccaggat	acaacagacc	cttgctcgct	240
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caggaatatac	tgttcccagc	ccctccccc	tcagggccag	gagtccaggc	ccccagcccc	780
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cagtcccccc	ttgtggcacg	ttgacccaa	cttaccagtt	ggttttcat	ttttgtccc	1140
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<210> 226

<211> 119

<212> DNA

<213> Homo sapien

<400> 226

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<210> 227

<211> 818

<212> DNA

<213> Homo sapien

<400> 227

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acggacggtt	cttagcacaa	tttgtgaaat	ctgtgtaraa	ccggctttg	cagggagat	180
aattttcctc	ctctggagga	aagggtgtt	ttgacaggca	gggagacagt	gacaaggcta	240
gagaaagcca	cgctcggcct	tctctgaacc	aggatggac	ggcagacccc	tgaaaacgaa	300
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gacaggctct	gccctcaagc	cggctgaggg	cagcaaccac	tctccccc	tttctcacgc	660
aaagccatc	ccacaaatcc	agaccatacc	atgaagcaac	gagacccaaa	cagtttggct	720
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<212> DNA	
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accagattct aggccagttt gttccactga agctttccc acagcagtc acctctgcag	360
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ttcttttgtt taatgttct ctgtgttgc agctgttcc atttctggg ctaagcagca	660
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tgcagggtt ttgttttttta attattattt ttagaaacgt caccacagt ccctgttaat	180
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caatataaaag tcctgttca cactcaggaa cgagagctga cccagtaag ggagaagttt	180
cgggaaaggga gagatgcctc cctctcattt aatgagcatc tccaggccct cctcactcc	240
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g	301
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<213> Homo sapien

<400> 235

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tgctttact aatgtctctg aacttctgtc cctcttggtt catggatagt ccaataaata	180
atgttatctt tgaactgatg ctcataggag agaatataag aactctgagt gatatcaaca	240
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<210> 236

<211> 301

<212> DNA

<213> Homo sapien

<400> 236

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tcggagcagc atcattaata ccaaggcagaa tgctaatag ataaatacaa tggtatata	180
tggtagacg gtttcatgag tacagtgtac tggatgtatcg taatctggac ttgggttgt	240
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<210> 237

<211> 301

<212> DNA

<213> Homo sapien

<400> 237

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<210> 238

<211> 301

<212> DNA

<213> Homo sapien

<400> 238

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cctttagact tcggagtcg aggctctcca gggttccccca gcccatcaat cattttctgc	180
acccctgccc tggaaagcag ctcctgggg ggtggaaatg ggtgactaga agggatttca	240
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<211> 239

<212> DNA

<213> Homo sapien

<400> 239

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cataataacct	tagagatcaa	gaaacattt	cacagttcaa	ctgtttaaaa	atagctcaac	180
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<210> 240

<211> 300

<212> DNA

<213> Homo sapien

<400> 240

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gctgggtgag	ccagatgact	tctgttccct	ggtcactttc	ttcaatgggg	cgaatggggg	180
ctgccaggtt	tttaaaatca	tgcttcatct	tgaagcacac	ggtcacttca	ccctcctcac	240
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<210> 241

<211> 301

<212> DNA

<213> Homo sapien

<400> 241

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g						301

<210> 242

<211> 301

<212> DNA

<213> Homo sapien

<400> 242

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gtcttcaaga	atatatcatt	ccttttccac	tagaacccat	tcaaaatata	agtcagaat	180
cttaatataca	acaaatataat	caagcaaact	ggaaggcaga	ataactacca	taattttagta	240
taagtaccca	aagtttataa	aatcaaaaagc	cctaatgata	accattttta	gaattcaatc	300
a						301

<210> 243

<211> 301

<212> DNA

<213> Homo sapien

<400> 243

aggtaagtcc cagtttgaag	ctcaaaaagat	ctggtatgag	cataggctca	tcgacgacat	60
ggtggcccaa gctatgaaat	cagagggagg	cttcatctgg	gcctgtaaaa	actatgatgg	120
tgacgtgcag tcggactctg	tggcccaagg	gtatggctct	ctcggcatga	tgaccagcgt	180
gctggtttgt ccagatggca	agacagtaga	agcagaggct	gcccacggga	ctgtaacccg	240
tcactaccgc atgttccaga	aaggacagga	gacgtccacc	aatcccattg	cttccatttt	300
t					301

<210> 244
<211> 300
<212> DNA
<213> Homo sapien

<400> 244

gctggtttgc aagaatgaaa	tgaatgattc	tacagctagg	acttaacctt	gaaatggaaa	60
gtcatgcaat cccatttgc	ggatctgtct	gtgcacatgc	ctctgttagag	agcagcattc	120
ccagggacct tggaaaacagt	tgacactgta	aggtgcttgc	tccccaaagac	acatcctaaa	180
aggtgttgta atggtggaaa	cgttttcctt	cttatttgc	ccttcttatt	tatgtgaaca	240
actgtttgtc ttttgttat	ctttttttaaa	ctgtaaagtt	caattgtgaa	aatgaatatc	300

<210> 245
<211> 301
<212> DNA
<213> Homo sapien

<400> 245

gtctgagat taaaaatgtt	attgaaaatta	tcccaacca	atgttagaaa	agaaaagaggt	60
tatataactta gataaaaaat	gaggtgaatt	actatccatt	gaaatcatgc	tctttagaatt	120
aaggccagga gatattgtca	ttaatgtara	cttcaggaca	ctagagtata	gcagccctat	180
gttttcaaag agcagagatg	caattaaata	ttgttttagca	tcaaaaaggc	cactcaatac	240
agctaataaa atgaaagacc	taatttctaa	agcaattctt	tataatttac	aaagttttaa	300
g					301

<210> 246
<211> 301
<212> DNA
<213> Homo sapien

<400> 246

ggctgtcct acaatgcctg	cttcttgaaa	gaagtcggca	ctttctagaa	tagctaaata	60
acctggcctt attttaaaga	actatttgta	gctcagattg	gttttcttat	ggctaaaata	120
agtgccttctt gtggaaaatta	aataaaacag	ttaattcaaa	gccttgatat	atgttaccac	180
taacaatcat actaaatata	ttttgaagta	caaagttga	catgcctaa	agtgacaacc	240
caaatgtgtc ttacaaaaca	cgttcctaac	aaggtatgct	ttacactacc	aatgcagaaa	300
c					301

<210> 247
<211> 301
<212> DNA
<213> Homo sapien

<400> 247	
aggccttg gcagggctca tggatcagag ctcaaactgg agggaaaggc atttcgggta	60
gcctaagagg gcgactggcg gcagcacaaac caaggaaggc aaggttgtt ccccccacgct	120
gtgtcctgtg ttcatggcg acacacaatc ctcatggaa caggatcacc catgcgtgc	180
ccttcatgtat caaggttggg gcttaagtgg attaaggggag gcaagttctg ggttccttgc	240
ctttcaaac catgaagtca ggctctgtat ccctccttt ccttaactgtat attctaacta	300
a	301
<210> 248	
<211> 301	
<212> DNA	
<213> Homo sapien	
<400> 248	
aggccttgg agatgccatt tcagccgaag gactcttctw ttccgaaagta caccctcact	60
attaggaaga ttcttagggg taattttct gaggaggag aactagccaa cttaagaatt	120
acaggaagaa agtggttgg aagacagcca aaaaataaa agcagattaa attgtatcag	180
gtacattcca gcctgttggc aactccataa aaacattca gattttaatc ccgaatttag	240
ctaatgagac tggattttg tttttatgt tgtgtgtcg agagctaaaa actcagttcc	300
c	301
<210> 249	
<211> 301	
<212> DNA	
<213> Homo sapien	
<400> 249	
gtccagagga agcacctggt gctgaactag gcttgcctg ctgtgaactt gcacttggag	60
ccctgacgct gctgttctcc cgaaaaacc cgaccgacct ccgcgatctc cgtcccgccc	120
ccagggagac acagcgtga ctcagagctg gtcgcacact gtgcctccct cctcaccgccc	180
catcgtaatg aattattttgg aaaattaatt ccaccatccct ttcagattct ggatggaaag	240
actgaatctt tgactcagaa ttgtttgctg aaaagaatga tgtgactttc ttagtcattt	300
a	301
<210> 250	
<211> 301	
<212> DNA	
<213> Homo sapien	
<400> 250	
ggctgtgac aaggacttgc aggctgtggg aggaagtga cccttaacac tacacttctc	60
cttatcttta ttggcttgat aaacataatt atttctaaca ctagcttatt tccagttgcc	120
cataaggcaca tcagttacttt tctctggctg gaatagtaaa ctaaagtatg gtacatctac	180
ctaaaagact actatgtgga ataatacata ctaatgaagt attacatgtat ttaaagacta	240
caataaaacc aaacatgctt ataacattaa gaaaaacaat aaagatacat gattgaaacc	300
a	301
<210> 251	
<211> 301	
<212> DNA	
<213> Homo sapien	

<400> 251
 gccgagggtcc tacatggc ccagttccc cctgcacccct ctccagggcc cctgcctcat 60
 agacaaccc atagagcata ggagaactgg ttgcctggg ggcaggggaa ctgtctggat 120
 ggcaggggtc ctcaaaaatg ccactgtcac tgccaggaaa tgcttctgag cagtagacacct 180
 cattgggatc aatgaaaagc ttcaagaaat cttcaggctc actctcttga aggccccgaa 240
 cctctggagg gggcagtgg aatcccagct ccaggacgga tcctgtcgaa aagatatcct 300
 c 301

<210> 252
 <211> 301
 <212> DNA
 <213> Homo sapien

<400> 252
 gcaaccaatc actctgttc acgtgacttt tattaccata caatttggg catttcctca 60
 ttttctacat tgtagaatca agagtgtaaa taaatgtata tcgatgtctt caagaatata 120
 tcattcctt ttcacttagga acccattcaa aatataagtc aagaatctta atatcaacaa 180
 atatatcaag caaactggaa ggcagaataa ctaccataat ttagtataag tacccaaagt 240
 tttataaaatc aaaagcccta atgataacca tttttagaat tcaatcatca ctgtagaatc 300
 a 301

<210> 253
 <211> 301
 <212> DNA
 <213> Homo sapien

<400> 253
 ttccctaaga agatgttatt ttgttgggtt ttgttcccccc tccatctcga ttctcgta 60
 caactaaaaaaa aaaaaataa agaaaaaaatg tgctgcgttc tgaaaaataa ctccttagct 120
 tggtctgatt gtttcagac cttaaaatataaacttggtt cacaagctt aatccatgtg 180
 gatttttttt cttagagaac cacaacat aaaaggagca agtcggactg aatacctgtt 240
 tccatagtgcc cacagggta ttccctcacat ttctccata ggaaaaatgtt tttcccaag 300
 g 301

<210> 254
 <211> 301
 <212> DNA
 <213> Homo sapien

<400> 254
 cgctgcgcct ttccctggg ggaggggcaa ggccagaggg ggtccaagtg cagcacgagg 60
 aacttgacca attcccttga agcgggtggg ttaaaccctg taaatggaa caaaaatcccc 120
 ccaaatactt tcatcttacc ctggtgact cctgactgtt gaatttttg gttgaaacaa 180
 gaaaaaaaaata aagcttgaa ctttcaagg ttgcttaaca ggtactgaaa gactggcctc 240
 acttaaactg agccaggaaa agctgcagat ttattaatgg gtgtgttagt gtgcagtgcc 300
 t 301

<210> 255
 <211> 302
 <212> DNA

<213> Homo sapien

<400> 255
 agctttttt tttttttttt tttttttttt ttcattaaaa aatagtgctc tttattataa 60
 attactgaaa tgtttctttt ctgaatataa atataaatat gtgcaaagtt tgacttggat 120
 tgggattttg ttgagttctt caagcatctc ctaataccct caagggcctg agtagggggg 180
 aggaaaaagg actggaggtg gaatcttat aaaaaacaag agtgatttag gcagattgt 240
 aacattatta aaaaacaaga aacaaacaaa aaaatagaga aaaaaaccac cccaacacac 300
 aa 302

<210> 256
 <211> 301
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(301)
 <223> n = A,T,C or G

<400> 256
 gttccagaaa acattgaagg tggcttccca aagtctaact agggataaccc cctctagcct 60
 aggaccctcc tccccacacc tcaatccacc aaaccatcca taatgcaccc agataggccc 120
 acccccaaaa gcctggacac cttgagcaca cagttatgac caggacagac tcacatcttat 180
 aggcaaatacg ctgctggcaa actggcatta cctggtttgt ggggatgggg gggcaagtgt 240
 gtggcctctc ggcctggta gcaagaacat tcagggtagg cctaagttan tcgtgttagt 300
 t 301

<210> 257
 <211> 301
 <212> DNA
 <213> Homo sapien

<400> 257
 gttgtggagg aactctggct tgctcataa gtcctactga ttttcaactat cccctgaatt 60
 tccccactta ttttgtctt tcactatcgcc aggccttaga agaggtctac ctgcctccag 120
 tcttacctag tccagtctac cccctggagt tagaatggcc atcctgaagt gaaaagtaat 180
 gtcacattac tcccttcagt gatttcttgt agaagtgcac atccctgaat gccacccaaga 240
 tcttaatctt cacatctta atcttatctc tttgactcct ctttacaccg gagaaggctc 300
 C 301

<210> 258
 <211> 301
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(301)
 <223> n = A,T,C or G

<400> 258
cagcagtagt agatgccgt a tgccagcacg cccagcactc ccaggatcatc caccagcacc 60
agggggcccaag ccaccaggcg cagaagcaag ataaacagta ggctcaagac cagagccacc 120
cccagggcaa caagaatcca ataccaggac tggcaaaaat cttcaaaagat cttaacactg 180
atgtctcggg cattgaggct gtcaataana cgctgatccc ctgctgtatg gtgtgtcat 240
tggtgatccc tgggagcgcc ggtggagtaa cgttggtcca tggaaagcag cgcccacaac 300
t 301

<210> 259
<211> 301
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G

<400> 259
tcatatatgc aaacaatgc agactangcc tcagggcagag actaaaggac atctcttggg 60
gtgtcctgaa gtgatttgga cccctgaggg cagacaccta agtaggaatc ccagtggaa 120
gcaaagccat aaggaagccc aggattcctt gtgatcagga agtggccag gaaggtctgt 180
tccagctcac atctcatctg catgcagcac ggaccggatg cgcccactgg gtcttggctt 240
ccctcccatc ttctcaagca gtgtccttgt tgagccattt gcattcattgg ctccaggtgg 300
c 301

<210> 260
<211> 301
<212> DNA
<213> Homo sapien

<400> 260
ttttttttct ccctaaggaa aaagaaggaa caagtctcat aaaaccaaata aagcaatgg 60
aagggtctt aactgaaaa agatttaggat tcactggtt acaagttata attgaatgaa 120
agaactgtaa cagccacagt tggccatttc atgccaatgg cagcaaacaa caggattaac 180
tagggcaaaa taaataagtg tgtggaaagcc ctgataagtg cttaataaac agactgatcc 240
actgagacat cagtacctgc ccgggcggcc gtcgagccg aattctgcag atatccatca 300
c 301

<210> 261
<211> 301
<212> DNA
<213> Homo sapien

<400> 261
aaatattcga gcaaattcctg taactaatgt gtctccataa aaggcttga actcagtgg 60
tctgcttcca tccacgattc tagcaatgac ctctcgac tcaaagctcc tcttaaggtt 120
agcaccaact attccataca attcatcagc aggaaataaa ggctcttcag aagttcaat 180
ggtgacatcc aatttcttct gataatttag attcctcaca accttccttag ttaagtgaag 240
ggcatgatga tcatccaaag cccagtggc acttactcca gactttctgc aatgaagatc 300
a 301

<210> 262		
<211> 301		
<212> DNA		
<213> Homo sapien		
<400> 262		
gaggagagcc tgttacagca tttgttaagca cagaataactc caggagtatt tgtaattgtc	60	
tgtgagcttc ttgcgcgaag tctctcagaa attaaaaag atgcaaatcc ctgagtcacc	120	
cctagacttc ctaaacccaga tcctctgggg ctggAACCTG gcactctgca tttgtaatga	180	
gggcTTTCTG gtgcacacct aattttgtgc atcttgcCC taaatCCTGG attagtGCC	240	
catcattacc cccacattat aatgggatag attcagagca gatactctcc agcaaagaat	300	
c	301	
<210> 263		
<211> 301		
<212> DNA		
<213> Homo sapien		
<220>		
<221> misc_feature		
<222> (1)...(301)		
<223> n = A,T,C or G		
<400> 263		
tttagcttgt ggttaatgac tcacaaaact gattttaaaa tcaagttaat gtgaattttg	60	
aaaattacta cttaatccta attcacaata acaatggcat taaggTTGA CTTGAGTTGG	120	
ttcttagtat tattttatggt aaataggctc ttaccacttg caaataactg gccacatcat	180	
taatgactga ctcccAGTA aggctctcta agggtaagt angaggatcc acaggatttg	240	
agatgctaag gccccAGAGA tcgtttgatc caacccttta attttcagag gggAAAATGG	300	
g	301	
<210> 264		
<211> 301		
<212> DNA		
<213> Homo sapien		
<400> 264		
aaagacgtta aaccactcta ctaccacttg tggaactctc aaaggtaaaa tgacAAASCC	60	
aatgaatgac tctaaaaaca atatTTACAT ttaatggTTT gtagacaata aaaaaACAAG	120	
gtggatagat ctagaattgt aacattttaa gaaaaccata scatttgaca gatgagaaAG	180	
ctcaattata gatgcaaAGT tataactaaa ctactatAGT agtaaAGAAA tacatttcac	240	
acccttcata taaattcact atcttggctt gaggcactcc ataaaatgtA tcacgtgcat	300	
a	301	
<210> 265		
<211> 301		
<212> DNA		
<213> Homo sapien		
<400> 265		

tgc	ccaaagt	atgtgtaagt	gtatccgcac	ccagaggtaa	aactacactg	tcatcttgc	60
ttt	cggta	cgcagtattt	cttcctggg	gagaagccgg	gaagtcttct	cctggctcta	120
ca	atttcttgc	gaagtctcta	atcaactttt	gttccatttg	tttcatttct	tcaaggaggaa	180
ttt	cggat	gtcaacatgt	tctctaacaa	cactgccc	tttctgtaaa	gaatccaaag	240
c	agtc	tttgacatg	tcaacaacca	gcataactag	agtatcottc	agagatacgg	300
							301

<210> 266
<211> 301
<212> DNA
<213> Homo sapien

		<400> 266				
taccgtctgc	ccttcctccc	atccaggcca	tctgcgaatc	tacatgggtc	ctcctattcg	60
acaccagatc	actctttcct	ctacccacag	gcttgctatg	agcaagagac	acaacctcct	120
ctcttctgtg	ttccagcttc	tttcctgtt	cttcccaccc	cttaagttct	attcctgggg	180
atagagacac	caatacccat	aacctcttc	ctaagcctcc	ttataaccca	gggtgcacag	240
cacagactcc	tgacaactgg	taaggccaat	gaactgggag	ctcacagctg	gctgtgcctg	300
a						301

<210> 267
<211> 301
<212> DNA
<213> Homo sapien

		<400> 267				
aaagagcaca	ggccagctca	gcctgccctg	gccatctaga	ctcagcctgg	ctccatgggg	60
gttctcagtg	ctgagtcct	ccagggaaaag	ctcacctaga	ccttctgagg	ctgaatcttc	120
atcctcacag	gcagcttctg	agagcctgat	attcctagcc	ttgatggct	ggagtaaagc	180
ctcattctga	ttccctctcct	tcttttcttt	caagttggct	ttcctcacat	ccctctgttc	240
aattcgcttc	agcttgtctg	ctttagccct	catttccaga	agcttcttct	cttggcata	300
t						301

<210> 268
<211> 301
<212> DNA
<213> Homo sapien

		<400> 268				
aatgtctcac	tcaactactt	cccagcctac	cgtggcctaa	ttctggagt	tttcttctta	60
gatcttggga	gagctggttc	ttctaaggag	aaggaggaag	gacagatgta	actttggatc	120
tcgaagagga	agtctaattgg	aagtaattag	tcaacggtcc	ttgttttagac	tcttggaaata	180
tgctgggtgg	ctcagtgagc	cctttggag	aaagcaagta	ttattcttaa	ggagtaacca	240
cttcccatttgc	ttctactttc	taccatcatc	aattgtatata	tatgtattct	ttggagaact	300
a						301

<210> 269
<211> 301
<212> DNA
<213> Homo sapien

<400> 269

taacaatata cactagctat	cttttaact gtccatcatt	agcaccaatg aagattcaat	60
aaaattacct ttattcacac	atctcaaaac aattctgcaa	attcttagtg aagtttaact	120
atagtacag accttaaata	ttcacattgt tttctatgtc	tactgaaaat aagttcacta	180
cttttctgga tattcttac	aaaatcttat taaaattcct	ggtattatca cccccaatta	240
tacagtagca caaccacett	atgtatgttt tacatgatag	ctctgtagaa gtttcacatc	300
t			301

<210> 270

<211> 301

<212> DNA

<213> Homo sapien

<400> 270

cattgaagag ctttgcgaa acatcagaac acaagtgc	tt ataaaattaa ttaagcctta	60
cacaagaata catattcctt ttatttctaa ggagttaaac	atagatgttag ctgatgtgga	120
gagttgctg gtgcagtgc	tattggataa cactattcat	180
ccaactcctt gaactggatc	atcagaagaa gggtggtgc	240
tggaccaacc aactaaattc	cgatatactg cactagataa	300
a	ctctaccagg ctgtatcagt	301

<210> 271

<211> 301

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(301)

<223> n = A,T,C or G

<400> 271

aaaaggttct cataagatta acaatttaaa taaatatttg	atagaacatt ctttctcatt	60
tttatagctc atcttaggg ttgatattca	gttcatgctt ccctgctgt tcttgatcca	120
gaattgcaat cactcatca	gcctgtattc gctccaattc	180
tgaaccacag agccacagca	tctataaaagt gggccaagg	240
ttcttcctcc agatganaac	cacctttc ctttgtgac	300
c	tgccttcacc ccatganggt	301

<210> 272

<211> 301

<212> DNA

<213> Homo sapien

<400> 272

taaattgcta agccacagat aacaccaatc	aaatggaaca aatcactgtc	ttcaaatgtc	60
ttatcagaaa accaaatgag	cctggaatct tcataatacc	taaacatgcc	120
tccaaataatt	ccctcatgtat gagcaagaaa	aattctttgc	180
gcatcttc	aacatttgagt ggctctgt	aatctatgtt	240
ctaaggactt	ccattgcattc tcctacaata	tttctctac	300
g	gcaccactag aattaagcag		301

<210> 273
<211> 301
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G

<400> 273

acatgtgtgt atgtgttatct ttggaaaaan aanaagacat cttgttayt attttttgg	60
agagangctg ggacatggat aatcacwtaa tttgctayta tyacttaat ctgactyga	120
gaaccgtcta aaaataaaat ttaccatgtc dtatattcct tatagtatgc ttatccacc	180
ttytttctgt ccagagagag ttcgtgac ananatttma gggtaamac atgmattgg	240
gggacttny tttacngagm accctgcccc sgcccccctcg makcngantt ccgcsananc	300
t	301

<210> 274
<211> 301
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G

<400> 274

cttatataact ctttctcaga ggcaaaagag gagatggta atgtagacaa ttcttgagg	60
aacagtaaat gattattaga gagaangaat ggaccaagga gacagaaaatt aacctgtaaa	120
tgattctctt tggaatctga atgagatcaa gaggccagct ttagcttg gaaaagtcca	180
tcttaggtatg gttgcattct cgtcttctt tctgcagtag ataatgaggt aaccgaaggc	240
aattgtgctt ctttgataa gaagcttct tggcatatc agggaaattcc aganaaaagtc	300
c	301

<210> 275
<211> 301
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G

<400> 275

tcgggtgtca cggcacgtgg cattgaacat tgcaatgtgg agcccaaacc acagaaaaatg	60
gggtgaaatt ggccaaactt ctattaactt atgttggcaa tttgccacc aacagtaagc	120
tggcccttct aataaaagaa aattgaaagg tttctacta aacgaaatta agtagtggag	180

tcaagagact cccaggcctc agcgtaacctg cccgggcggc cgctcgaagc cgaattctgc	240
agatatccat cacactggcg gncgctgan catgcatcta gaaggnccaa ttgcgcstat	300
a	301
<210> 276	
<211> 301	
<212> DNA	
<213> Homo sapien	
<400> 276	
tgtacacata ctcataaaat aaatgactgc attgtggtat tattactata ctgattatat	60
ttatcatgtg acttctaatt agaaaatgtt tccaaaagca aaacagcaga tataaaaaat	120
taaagagaca gaagatagac attaacagat aaggcaactt atacatttgag aatccaaatc	180
caatacattt aaacatttgg gaaatgaggg ggacaaatgg aagccagatc aaatttgtgt	240
aaaactattc agtatgtttc ccttgcttca tgtctgagaa ggctctcctt caatggggat	300
g	301
<210> 277	
<211> 301	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1)...(301)	
<223> n = A,T,C or G	
<400> 277	
tttgttgcgt tcagtatttt attacttgcg ttatgagtgc tcacctggaa aattctaaag	60
atacagagga cttggaggaa gcagagcaac tgaatttaat taaaagaag gaaaacattg	120
gaatcatggc actcctgata cttcccaaa tcaacactct caatgccca ccctcgctct	180
caccatagtg gggagactaa agtggccacg gatttgcctt angtgtgcag tgcgttctga	240
gttcnctgtc gattacatct gaccagtctc cttttccga agtccntccg ttcaatcttg	300
c	301
<210> 278	
<211> 301	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1)...(301)	
<223> n = A,T,C or G	
<400> 278	
taccactaca ctccaggcctg ggcaacagag caagacctgt ctcaaagcat aaaatggaat	60
aacatatacaa atgaaacagg gaaaatgaag ctgacaattt atgaaagcca gggcttgtca	120
cagtctctac tggttattatg cattacctgg gaatttataat aagcccttaa taataatgcc	180
aatgaacatc tcatgtgtgc tcacaatgtt ctggcactat tataagtgtc tcacaggttt	240
tatgtgttct tcgttaacttt atggantagg tactcgcccg cgaacacgct aagccgaatt	300

c

301

<210> 279
<211> 301
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G

<400> 279

aaagcaggaa tgacaaagct tgctttctg gtatgttcta ggtgtattgt gactttact	60
gttatattaa ttgccaatat aagtaaatat agattatata tgtatagtgt ttcaccaaagc	120
ttagacctt accttccagc caccccacag tgcttgatat ttcagagtca gtcattggtt	180
atacatgtgt agttccaaag cacataagct agaanaanaa atatttctag ggagcactac	240
catctgttt cacatgaaaat gcccacacaca tagaactcca acatcaattt cattgcacag	300
a	301

<210> 280
<211> 301
<212> DNA
<213> Homo sapien

<400> 280

ggtactggag tttccctccc ctgtaaaaac gtaactactg ttgggagtga attgaggatg	60
tagaaagggtg gtggAACCAA attgtggtca atggaaatag gagaatatgg ttctcaactct	120
tgagaaaaaaaaa acctaagatt agcccaggta gttgcctgta acttcagttt ttctgcctgg	180
gtttgatata gtttagggtt ggggttagat taagatctaa attacatcg gacaaagaga	240
cagactattta actccacagt taattaagga ggtatgttcc atgttttattt gttaaagcag	300
t	301

<210> 281
<211> 301
<212> DNA
<213> Homo sapien

<400> 281

aggtaacaaga agggaaatgg gaaagagctg ctgctgtggc attgttcaac ttggatattc	60
gccgagcaat ccaaattctg aatgaagggg catcttctga aaaaggagat ctgaatctca	120
atgtggtagc aatgcttta tcgggttata cgatgagaa gaactccctt tggagagaaa	180
tgtgttagcac actgcgatta cagctaaata acccgattt gtgtgtcatg tttgcatttc	240
tgacaagtga aacaggatct tacgatggag ttttgtatga aaacaaagtt gcagttacctc	300
g	301

<210> 282
<211> 301
<212> DNA
<213> Homo sapien

<400> 282
caggtactac agaattaaaa tactgacaag caagtagttt cttggcgtgc acgaattgca 60
tccagaaccc aaaaattaag aaattcaaaa agacatttg tggcacctg ctagcacaga 120
agcgcagaag caaagcccag gcagaaccat gctaacctta cagctcagcc tgcacagaag 180
cgcagaagca aagcccaggc agaaccatgc taacccttaca gctcagcctg cacagaagcgc 240
cagaagcaaa gcccaggcag aacatgctaa cttacagct cagcctgcac agaagcacag 300
a 301

<210> 283
<211> 301
<212> DNA
<213> Homo sapien

<400> 283
atctgtatac ggcagacaaa ct当地tarag tgttagagagg tgagcgaaag gatgcaaaag 60
cactttgagg gcttataat aatatgctgc ttgaaaaaaaaaa aaatgtgtag ttgatactca 120
gtgcatactcc agacatagta aggggttgct ctgaccaatc aggtgatcat ttttctatc 180
acttcccagg ttttatgcaa aaattttgtt aaattctata atggtgatat gcatcttta 240
ggaaacatat acattttaa aaatctatcc tatgtaagaa ctgacagacg aatttgcttt 300
9 301

<210> 284
<211> 301
<212> DNA
<213> Homo sapien

<400> 284
caggtacaaa acgttattaa gtggcttatac atttgaacat ttgtggctt tattttacttt 60
gcttcgttg tggccaaagc aacatcttcc ctaaatatata attaccaaga aaagcaagaa 120
gcagattagg ttttgacaa aacaaacagg cccaaagggg gctgaccctgg agcagagcat 180
ggtgagagggc aaggcatgag agggcaagtt tggtgtggac agatctgtgc ctactttatt 240
actggatgaa aagaaaacaa agttcatttga tgtcgaagga tatatacagt gtttagaaatt 300
a 301

<210> 285
<211> 301
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G

<400> 285
acatcaccat gatggatcc cccacccatt atacgttgta tgtttacata aatactttc 60
aatgatcatt agtggatcata aaaaaatact gaaaactcct tctgcataccc aatctctaacc 120
cagggaaagca aatgttattt acagacctgc aagccctccc tcaaacnaaa ctatctgg 180
attaaatatg tctgacttct tttgagggtca cacgactagg caaatgctat ttacgtatcg 240
caaaaagctgt ttgaagagtc aaagccccca tgtgaacacag atttctggac cctgtacacag 300
t 301

<210> 286
 <211> 301
 <212> DNA
 <213> Homo sapien

<400> 286
 taccactgca ttccagcctg ggtgacagag tgagactccg tctccaaaaaa aaaccttgct
 tgttatattat tttgcctta cagtggatca ttcttagttagg aaaggacagt aagattttt
 atcaaaaatgt gtcatgccag taagagatgt tatattctt tctcatttct tccccaccca
 aaaataagct accatatagc ttataagtct caaattttg cctttacta aaatgtgatt
 gtttctgttc attgtgtatg cttcatcacc tatattaggc aaattccatt tttcccttg
 t

60
120
180
240
300
301

<210> 287
 <211> 301
 <212> DNA
 <213> Homo sapien

<400> 287
 tacagatctg ggaactaaat attaaaaatg agtgtggctg gatatatgga gaatgttggg
 cccagaagga acgttagagat cagatattac aacagcttg ttttgagggtagaaatatg
 aaatgatttg gttatgaacg cacagtttag gcagcaggc cagaatcctg accctctgcc
 ccgtggttat ctcccccac gcttggctgc ctcatgttat cacagtattc catttgttt
 gttgcatgtc ttgtgaagcc atcaagattt ttcgtctgt tttcctctca ttggtaatgc
 t

60
120
180
240
300
301

<210> 288
 <211> 301
 <212> DNA
 <213> Homo sapien

<400> 288
 gtacacctaa ctgcaaggac agctgaggaa tgtaatgggc agccgctttt aaagaagtag
 agtcaatagg aagacaattt ccagttccag ctcagtctgg gtatctgcaa agctgcaaaa
 gatctttaaa gacaatttca agagaatatt tccttaaagt tggcaatttg gagatcatac
 aaaagcatct gctttgtga tttaatttag ctcatctggc cactggaaga atccaaacag
 tctgccttaa ttttggatga atgcattatg gaaattcaat aatttagaaa gttaaaaaaaa
 a

60
120
180
240
300
301

<210> 289
 <211> 301
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(301)
 <223> n = A,T,C or G

<400> 289

ggtacactgt ttccatgtta tgtttctaca cattgctacc tcagtgcgtcc tggaaactta	60
gcttttgatg tctccaagta gtccacccctc atttaactct ttgaaactgt atcatctttg	120
ccaagtaaga gtggggcct atttcagctg ctttgacaaa atgactggct cctgacttaa	180
cgttctataa atgaatgtgc tgaagcaaag tgcccatggt ggcggcgaan aagagaaaaga	240
tgtgttttgtt tttggactct ctgtggtccc ttccaatgct gtgggttcc aaccagngga	300
a	301
<210> 290	
<211> 301	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1)...(301)	
<223> n = A,T,C or G	
<400> 290	
acactgagct cttttgtata aatatacaga atgcttggca tatacaagat tctataactac	60
tgactgatct gttcatttct ctcacagctc ttaccccaa aagctttcc accctaagtg	120
ttctgacccctc cttttctaat cacagtaggg atagaggcgag anccacccatc aatgaacatg	180
gagttctatc aagaggcaga aacagcacag aatcccgat ttaccattcg ctagcagtgc	240
tgccttgaac aaaaacattt ctccatgtct cattttcttc atgcctcaag taacagttag	300
a	301
<210> 291	
<211> 301	
<212> DNA	
<213> Homo sapien	
<400> 291	
caggtaccaa tttttcttat cctagaaaca tttcattttt tgttgttcaa acataacaac	60
tatatcagct agatttttt tctatgcctt acctgctatg gaaaatttga cacattctgc	120
tttactcttt tgtttatagg tgaatcaca aatgtatttt tatgtattct gtatgttcaat	180
agccatggct gtttacttca tttaattttt ttagcataaaa gacattatga aaaggcctaa	240
acatgagctt cactccccca ctaactaatt agcatctgtt atttcttaac cgtaatgcct	300
a	301
<210> 292	
<211> 301	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1)...(301)	
<223> n = A,T,C or G	
<400> 292	
accttttagt agtaatgtct aataataaaat aagaatcaa ttttataagg tccatatacg	60
tgtattaaat aatttttaag tttaaaagat aaaataccat cattttaaat gttggattc	120

aaaacccaaag natataaccg aaaggaaaaa cagatgagac ataaaatgtat ttgcnagatg	180
ggaaatatacg tattttatgtat aattccatgtt ataatatgtgg ctacacactc	240
tcaactacaca cacagacccc acagtccat atgccacaaa cacattcca taacttgaaa	300
a	301
<210> 293	
<211> 301	
<212> DNA	
<213> Homo sapien	
<400> 293	
ggtagccaatgt gctgggtccgc gcctgttacc tgttctcaact gaaaagtctg gctaattgctc	60
tttgttagtc acttctgttattt ctgacaatca atcaatcaat ggccttagagc actgactgtt	120
aacacaaacg tcactagcaa agtagcaaca gctttaagtc taaatacaaaa gctgttctgt	180
gtgagaattttttttaaaaggc tacttgtata ataacccttg tcatttttaa tgtacctcg	240
cccgcgaccac gctaagccga attctgcaga tatccatcac actggcggcc gctcgagcat	300
g	301
<210> 294	
<211> 301	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1)...(301)	
<223> n = A,T,C or G	
<400> 294	
tgaccataa caatatacac tagctatctt tttaactgtc catcattagc accaatgaag	60
attcaataaa attaccttta ttccacacatc tcaaaaacaat tctgcaaattt cttagtgaag	120
tttaactata gtcacaganc ttaaatattt acattgtttt ctatgtctac tgaaaataag	180
ttcactactt ttctggata ttctttacaa aatcttatta aaattcctgg tattatcacc	240
cccaattata cagtagcaca accaccttat gtatgtttt catgatagtctgttagaggt	300
t	301
<210> 295	
<211> 305	
<212> DNA	
<213> Homo sapien	
<400> 295	
gtactctttc tctccccctcc tctgaattta attctttcaa ctgcattt gcaaggatta	60
cacatttacatc tttgtatgtat attgtgtgc aaaaaaaaaa gtgtcttgc ttaaaattac	120
ttgggttgc aatccatctt gctttttccc cattggact agtcattaaac ccattctgt	180
actggtagaa aaacrtctga agagctagtc tatcagcatc tgacaggtga attggatgg	240
tctcagaacc atttcaccca gacagcctgt ttctatcctg tttaataaaat tagttgggt	300
tctct	305
<210> 296	
<211> 301	

<212> DNA
<213> Homo sapien

<400> 296

aggtaactatg ggaagctgct	aaaataatat ttgatagtaa aagtatgtaa	tgtgcttatct	60
caccttagtag taaaactaaaa	ataaaactgaa actttatgga	atctgaagtt attttccttg	120
attaaataga attaataaac	caatatgagg aaacatgaaa	ccatgcaatc tactatcaac	180
tttggaaaaag tgattgaacg	aaccacttag ctttcagatg	atgaacactg ataagtcat	240
tgtcattact ataaatttta	aatctgtta ataagatggc	ctatagggag gaaaaagggg	300
C			301

<210> 297
<211> 300
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(300)
<223> n = A,T,C or G

<400> 297

actgagttt aactggacgc	caagcaggca aggctggaag	gttttgctct ctttgtgcta	60
aagggtttga aaaccttcaa	ggagaatcat tttgacaaga	agtacttaag agtctagaga	120
acaaaagangt gaaccagctg	aaagctctcg ggggaanctt	acatgtgttg ttaggcctgt	180
tccatcatcg ggagtgcact	ggccatccct caaaatttgc	ctgggctggc ctgagtggtc	240
accgcaccc	ggccgcgacc acgctaagcc	gaattctgca gatatccatc	300

<210> 298
<211> 301
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G

<400> 298

tatggggttt gtcacccaaa	agctgatgct gagaaaggcc	tccctggggc ccctcccgcg	60
ggcatctgag agacctggtg	ttccagtgtt tctggaaatg	ggtcccagtg ccgcggctg	120
tgaagctctc agatcaatca	cggaaaggcc ctggcggtgg	tggccacctg gaaccaccct	180
gtcctgtctg tttacatttc	actaycaggt tttctctggg	cattacnatt tggccccta	240
caacagtgac ctgtgcattc	tgctgtggcc tgctgtgtct	gcaggtggct ctcagcgagg	300
t			301

<210> 299
<211> 301
<212> DNA
<213> Homo sapien

<400> 299

gtttttagac	ggagttcac	tcttggcc	cagactggac	tgcaatggca	gggtctctgc	60
tcactgcacc	ctctgcctcc	caggcgag	caattctcct	gcctcagcct	cccaggttagc	120
tgggattgca	ggctcacgccc	accataccca	gctaattttt	ttgtattttt	agttagagacg	180
gagtttgcgc	atgttggcca	gctggtctca	aactcctgac	ctcaaggcgc	ctgcctgcct	240
cggcctccca	aagtgcgtgga	attataggca	tgagtcaaca	cggccagcct	aaagatattt	300
t						301

<210> 300
<211> 301
<212> DNA
<213> Homo sapien

<400> 300

attcagttt	atttgcgtcc	ccagtatctg	taaccaggag	tgccacaaaa	tcttgcaga	60
tatgtccac	acccactggg	aaaggctccc	acctggctac	ttccctctatc	agctgggtca	120
gctgcattcc	acaaggttct	cagcctaatg	agtttcaacta	cctgccagtc	tcaaaaactta	180
gtaaaagcaag	accatgacat	tcccccacgg	aaatcagagt	ttgccccacc	gtttgttac	240
tataaaggcct	gcctctaaca	gtccttgctt	ttcacaccca	atcccggagcg	catccccat	300
g						301

<210> 301
<211> 301
<212> DNA
<213> Homo sapien

<400> 301

ttaaattttt	gagaggataa	aaaggacaaa	taatctagaa	atgtgtcttc	ttcagtcgtc	60
agaggacccc	aggctccaa	gcaaccacat	ggtcaagggc	atgaataatt	aaaagttgg	120
gggaactcac	aaagaccctc	agagctgaga	cacccacaac	agtgggagct	cacaaagacc	180
ctcagagctg	agacacccac	aacagtggga	gctcacaaag	accctcagag	ctgagacacc	240
cacaacagca	cctcggttc	ctgcccacatg	tgtgaataag	gatgcaatgt	ccagaagtgt	300
t						301

<210> 302
<211> 301
<212> DNA
<213> Homo sapien

<400> 302

aggtacacat	ttagctgtg	gtaaatgact	cacaaaactg	atttaaaaat	caagttaatg	60
tgaatttga	aaattactac	ttaatcctaa	ttcacaataa	caatggcatt	aaggtttgac	120
ttgagtttgt	tcttagtatt	atttatggta	aataggctct	taccacttgc	aaataactgg	180
ccacatcatt	aatgactgac	ttcccagtaa	ggctctctaa	ggggtaagta	ggaggatcca	240
caggatttga	gatgctaagg	ccccagagat	cgtttgatcc	aaccctctta	ttttcagagg	300
g						301

<210> 303
<211> 301
<212> DNA
<213> Homo sapien

<400> 303

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aggtaccaac tgtgaaata ggttagaggat catttttct ttccatatca actaagtgt      60
atattgttt ttgacagttt aacacatctt ctctgtcag agattcttc acaaatgcac      120
tggctaatgg aactaccgct tgcattttaa aaatgggtt ttgtgaaatg atcataggcc      180
agtaacgggt atgttttct aactgatctt ttgctcggtt caaaggacc tcaagacttc      240
catcgatttt atatctgggg tctagaaaag gagttaatct gtttccttc ataaattcac      300
c                                         301

```

<210> 304
<211> 301
<212> DNA
<213> Homo sapien

<400> 304

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acatggatgt tattttgcag actgtcaacc tgaatttcta tttgcttgac attgcctaatt     60
tatttagttc agttcagct tacccacttt ttgtctgcaa catgcaraas agacagtgcc     120
cttttttagt tatacatatca ggaatcatct cacattggtt tgcatttgcattt ctggcagt     180
gactttcagc cactgggtt aggtggagtt ggccatatgt ctccactgca aaattactga     240
ttttccctttt gtaattaata agtgtgtgtt tgaagattct ttgagatgag gtatataatct    300
c                                         301

```

<210> 305
<211> 301
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G

<400> 305

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gangtacagc gtggcaagg taacaagaag aaaaaatgt gagtggcatc ctggatgag      60
cagggggaca gacctggaca gacacgttgc catttgcattt tgggttggggaaaatggcg      120
taaaggagga gaaacagata caaaatctcc aactcgttat taaggtattt tcattgcctag      180
aatattggta gaaacaagaa tacattcata tggcaaataa ctaaccatgg tggaaacaaaa      240
ttctgggatt taagttggat accaangaaa ttgttattttt agagctgttc atgaaataag      300
a                                         301

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<210> 306
<211> 8
<212> PRT
<213> Homo sapien

<400> 306

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Val Leu Gly Trp Val Ala Glu Leu
1          5

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<210> 307
<211> 637

<212> DNA

<213> Homo sapien

<400> 307

acagggratg aaggaaagg gagaggatga ggaagccccc	ctggggattt ggtttggtcc	60
ttgtgatcag gtggctatg gggcttatcc ctacaaagaa	aatccagaa ataggggcac	120
attgaggaat gatacttgag cccaaagagc attcaatcat	tgttttattt gccttmttt	180
cacaccattg gtgagggagg gattaccacc ctggggttat	gaagatggtt gaacacccca	240
cacatagcac cgagatatg agatcaacag tttcttagcc	atagagattc acagccccaga	300
gcaggaggac gcttcacac catgcaggat gacatgggg	atgcgctcg gattggtgtg	360
aagaagcaag gactttaga ggcaggctt atagtaacaa	gacggtgaaa caaactctga	420
tttccgtggg ggaatgtcat ggtcttgctt tactaagttt	ttagactggc aggtagtgaa	480
actcattagg ctgagaacct tttggatgc acttgacc	sctgataagag gaagtagcca	540
gttgggagcc ttcccagtg ggtgtggac atatctggca	agattttgtg gcactcctgg	600
ttacagatac tgggcagca aataaaaactg aatcttg		637

<210> 308

<211> 647

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(647)

<223> n = A,T,C or G

<400> 308

acgattttca ttatcatgt aatcggtca ctcaaggggc	caaccacagc tgggagccac	60
tgctcagggg aaggttcata tggactt tcactgccc	aa gttctatac aggatataaa	120
ggngcctcac agtatacata tggtagcaaa gaagaagaaa	caaacaactga tctcttctg	180
ccaccctctt gacccttgg aactcctctg accctttaga	acaacccctac ctaatatctg	240
ctagagaaaa gaccaacaac ggcctcaaa gatctttac	catgaaggc tcagctaatt	300
cttggcttaag atgtgggtt cacatttagt tctgaatatg	gggggaaggg tcaatttgct	360
cattttgtgt gtggataaaag tcaggatgcc cagggccag	agcagggggc tgcttgctt	420
gggaacaatg gctgacata taaccatagg ttatgggaa	caaaacaaca tcaaagtac	480
tgtatcaatt gccatgaaga cttgagggac ctgaatctac	cgattcatct taaggcagca	540
gaccaggattt gatggcaac aatgcagcag cagaatcaat	ggaaacaaca gaatgattgc	600
aatgtccttt ttttctctt gcttctgact tgataaaaagg	ggaccgt	647

<210> 309

<211> 460

<212> DNA

<213> Homo sapien

<400> 309

actttatagt ttaggctgga cattggaaaa aaaaaaaaa	acagaacaaca tgtgatagat	60
aatatgattt gctgcacact tccagactga tgaatgtat	acgtgatgga ctattgtat	120
gagcacatct tcagaagag gggaaatac tcattttt	tggccagcag ttgtttgatc	180
acccaaacatc atgcagaat actcagcaaa cttcttagc	tcttgagaag tcaaagtccg	240
ggggaaattt ttcctggcaa tttaattgg actcctttag	tgagagcagc ggctacccag	300
ctgggggtggt ggagcgaacc cgtcaactgt ggacatgcag	tggcagagct cctggtaacc	360

acctagagga atacacaggc acatgtgtga tgccaagcgt gacacctgta gcactcaa	420
ttgtcttgg tttgtcttc ggtgtgtaa attcttaagt	460
<210> 310	
<211> 539	
<212> DNA	
<213> Homo sapien	
<400> 310	
acgggactta tcaaataaaag ataggaaaag aagaaaaactc aaatattata ggcagaaaatg	60
ctaaagggtt taaaatatgt caggattgga agaaggcatg gataaagaac aaagttcagt	120
taggaaagag aaacacagaa ggaagagaca caataaaaagt cattatgtat tctgtgagaa	180
gtcagacagt aagatttgtg ggaaatgggt tgggttggtg tatggtatgt atttttagcaa	240
taatctttat ggcagagaaa gctaaaatcc tttagcttgc gtgaatgatc acttgctgaa	300
tccctcaagg taggcatgtat gaaggagggt ttagaggaga cacagacaca atgaactgac	360
ctagatagaa agccttagta tactcagcta ggaatagtga ttctgagggc acactgtgac	420
atgattatgt cattacatgt atggtagtga tggggatgtat aggaaggaag aactttaggc	480
atattttcac ccccacaaaaa gtcagttaaa tattggaca ctaaccatcc aggtcaaga	539
<210> 311	
<211> 526	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1)...(526)	
<223> n = A,T,C or G	
<400> 311	
caaattttgag ccaatgacat agaattttac aaatcaagaa gcttattctg gggccatttc	60
ttttgacgtt ttctctaaac tactaaagag gcattaatga tccataaattt atattatcta	120
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tctctttaca gggagctcct gcagcccccta cagaaaatgag tggctgagat tcttgattgc	420
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<210> 312	
<211> 500	
<212> DNA	
<213> Homo sapien	
<220>	
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<222> (1)...(500)	
<223> n = A,T,C or G	
<400> 312	

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ccatttctct	ttcccttcca	cctgccagtt	ttgctgactc	tcaacttgtc	atgagtgtaa	180
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gcttcttagg	aaaatatttt	tcttccaaaa	tcaagtaggaa	atctaaactt	atcccccttt	300
tgcagatgtc	tagcagcttc	agacatttg	ttaagaaccc	atgggaaaaaa	aaaaaatcct	360
tgctaattgt	gtttcctttg	taaaccanga	ttcttatttg	nctggtatag	aatatcagct	420
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<210>	313					
<211>	718					
<212>	DNA					
<213>	Homo sapien					
<220>						
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<222>	(1)...(718)					
<223>	n = A,T,C or G					
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<212>	DNA					
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<400>	314					
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<210>	315					
<211>	341					
<212>	DNA					
<213>	Homo sapien					

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gaccggcatt ctgaagatgt ctggAACCTC taccaggcagg atgatgatag ccccaatgac 180
agtccaccaggc tccccgacca gccggatatac gtccttaggg gtcatgtagg cttccctgaag 240
tagcttctgc tgtaagaggg ttttgtcccg ggggctcggt cggttattgg tcctggcctt 300
gaggggggcgg tagatgcagc acatggtgaa gcagatgtat t 341

<210> 316
<211> 151
<212> DNA
<213> Homo sapien

<400> 316
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tgtggccctt tctcgagttt ctgattataa acaccactgg agcgatgtgt tgactggact 120
cattcaggga gctctgggtt caatattat t 151

<210> 317
<211> 151
<212> DNA
<213> Homo sapien

<400> 317
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atcttcattt atctctggcc ttaaccctgg ctcctgaggc tgccggccagc agatcccagg 120
ccagggtctt gtttttgcac cacctgtttt a 151

<210> 318
<211> 151
<212> DNA
<213> Homo sapien

<400> 318
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tggggggcggt ttatcaggca gtgataaaaca t 151

<210> 319
<211> 151
<212> DNA
<213> Homo sapien

<400> 319
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catagatagt actaggtatt aatagatatg taaagaaaaga aatcacacca ttaataatgg 120
taagattggg tttatgtat tttatgtgg a 151

<210> 320
<211> 150

<212> DNA
<213> Homo sapien

<400> 320
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gagcggtctgc cctttttttt tttttttttt gggggaaatt tttttttttt aatagttatt
gagtgttctca cagcttacag taaataccat 120
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<210> 321
<211> 151
<212> DNA
<213> Homo sapien

<400> 321
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tgcctctgag aaatcaaagt cttcatacac t 120
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<210> 322
<211> 151
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(151)
<223> n = A,T,C or G

<400> 322
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attgtgcagg gtcgcttca nacttccagt t 120
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<210> 323
<211> 151
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(151)
<223> n = A,T,C or G

<400> 323
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nagactcant tactaccagg tttgtggttt twtgggagaa atgttaactgg acagtttagct
gttcaatyaa aaagacactt ancccatgtg g 120
 151

<210> 324
<211> 461
<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1) ... (461)

<223> n = A,T,C or G

<400> 324

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agagttacta cgaatcccat ctggttcca	gctatatcac tgacagcatg	gtagaagact	180
gcgaacctca cttcttagact ttacgggtgg	gacgaaacgg gttcagaaac	tgcaggggc	240
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cacacaaatg caatagttgg tcactgcatt	tttacctgaa ccaaagctaa	accgggttt	360
gccaccatgc accatggcat gccagagttc	aacactgttgc tcttggaaaa	ttgggtctga	420
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<210> 325

<211> 400

<212> DNA

<213> Homo sapien

<400> 325

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tctataaaatg aatgtgctga agcaaagtgc	ccatgggtggc ggcgaagaag	agaaaagatgt	240
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<210> 326

<211> 1215

<212> DNA

<213> Homo sapien

<400> 326

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<211> 220
<212> PRT
<213> Homo sapien

<400> 327		
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Leu Ser Ala Ala His Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu Gly		
35	40	45
Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met Val Glu		
50	55	60
Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Pro Leu Leu Ala		
65	70	75
Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu Ser Asp		
85	90	95
Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala Gly Asn		
100	105	110
Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly Arg Met Pro		
115	120	125
Thr Val Leu Gln Cys Val Asn Val Ser Val Val Ser Glu Glu Val Cys		
130	135	140
Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe Cys Ala Gly		
145	150	155
Gly Gly Gln Asp Gln Lys Asp Ser Cys Asn Gly Asp Ser Gly Gly Pro		
165	170	175
Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe Gly Lys Ala		
180	185	190
Pro Cys Gly Gln Val Gly Val Pro Gly Val Tyr Thr Asn Leu Cys Lys		
195	200	205
Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Ala Ser		
210	215	220

<210> 328
<211> 234
<212> DNA
<213> Homo sapien

<400> 328		
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atccgcagtg ggtgctgtca gccacacact gtttccagaa ctcctacacc atcgggctgg	180
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<210> 329	
<211> 77	
<212> PRT	
<213> Homo sapien	
<400> 329	
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Phe Cys Ser Gly Val Leu Val His Pro Gln Trp Val Leu Ser Ala Thr	
35 40 45	
His Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu Gly Leu His Ser Leu	
50 55 60	
Glu Ala Asp Gln Glu Pro Gly Ser Gln Met Val Glu Ala	
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<210> 330	
<211> 70	
<212> DNA	
<213> Homo sapien	
<400> 330	
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gctgcagcca	70
<210> 331	
<211> 22	
<212> PRT	
<213> Homo sapien	
<400> 331	
Gln His Asn Gly Pro Ile Pro Ser Leu Thr Pro Pro Ser Gly Ser Leu	
1 5 10 15	
Val Ser Gly Ser Cys Ser	
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<210> 332	
<211> 2507	
<212> DNA	
<213> Homo sapien	
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 <211> 3030
 <212> DNA
 <213> Homo sapien

<400> 333						
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<400> 334

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<210> 336

<211> 147

<212> PRT

<213> Homo sapien

<400> 336
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 35 40 45
 Val Ile Glu Leu Glu Arg Lys Phe Ser His Gln Lys Tyr Leu Ser Ala
 50 55 60
 Pro Glu Arg Ala His Leu Ala Lys Asn Leu Lys Leu Thr Glu Thr Gln
 65 70 75 80
 Val Lys Ile Trp Phe Gln Asn Arg Arg Tyr Lys Thr Lys Arg Lys Gln
 85 90 95
 Leu Ser Ser Glu Leu Gly Asp Leu Glu Lys His Ser Ser Leu Pro Ala
 100 105 110
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 Ala Phe Trp
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 <212> PRT
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<400> 337
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<210> 338
 <211> 9
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 Ala Asn Thr Gly Ile Gly Lys Glu Thr Ala Lys Glu Leu Ala Gln Arg
 50 55 60
 Gly Ala Arg Val Tyr Leu Ala Cys Arg Asp Val Glu Lys Gly Glu Leu
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 Val Ala Lys Glu Ile Gln Thr Thr Gly Asn Gln Gln Val Leu Val
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 Arg Lys Leu Asp Leu Ser Asp Thr Lys Ser Ile Arg Ala Phe Ala Lys
 100 105 110
 Gly Phe Leu Ala Glu Glu Lys His Leu His Val Leu Ile Asn Asn Ala
 115 120 125
 Gly Val Met Met Cys Pro Tyr Ser Lys Thr Ala Asp Gly Phe Glu Met
 130 135 140
 His Ile Gly Val Asn His Leu Gly His Phe Leu Leu Thr His Leu Leu
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 Leu Glu Lys Leu Lys Glu Ser Ala Pro Ser Arg Ile Val Asn Val Ser
 165 170 175
 Ser Leu Ala His His Leu Gly Arg Ile His Phe His Asn Leu Gln Gly
 180 185 190
 Glu Lys Phe Tyr Asn Ala Gly Leu Ala Tyr Cys His Ser Lys Leu Ala
 195 200 205
 Asn Ile Leu Phe Thr Gln Glu Leu Ala Arg Arg Leu Lys Gly Ser Gly
 210 215 220
 Val Thr Thr Tyr Ser Val His Pro Gly Thr Val Gln Ser Glu Leu Val
 225 230 235 240
 Arg His Ser Ser Phe Met Arg Trp Met Trp Trp Leu Phe Ser Phe Phe
 245 250 255
 Ile Lys Thr Pro Gln Gln Gly Ala Gln Thr Ser Leu His Cys Ala Leu
 260 - 265 270
 Thr Glu Gly Leu Glu Ile Leu Ser Gly Asn His Phe Ser Asp Cys His
 275 280 285
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<210> 340

<211> 483

<212> DNA

<213> Homo sapien

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<213> Homo sapien

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<210> 345
<211> 251
<212> DNA
<213> Homo sapien

<400> 345

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<210> 346
<211> 282
<212> DNA
<213> Homo sapien

<220>
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<222> (1)...(282)
<223> n = A,T,C or G

<400> 346

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<210> 347
<211> 201
<212> DNA
<213> Homo sapien

<220>
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<222> (1)...(201)
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<211> 251
<212> DNA
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<400> 348
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 gcccgcctc c 251

<210> 349
<211> 251
<212> DNA
<213> Homo sapien

<400> 349
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<211> 908
<212> DNA
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<400> 350
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<400> 355						
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gtgactttcc	cacggccaaa	aagctgtca	cacccacgc	acctctgtgc	ctcagttgc	420
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<210> 356
<211> 574
<212> DNA
<213> Homo sapien

<400> 356						
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caagcttccc	attttagat	ctcagtgcct	atgagtatct	gacacctgtt	cctctcttca	180
gtctctttagg	gaggcttaaa	tctgtctcag	gtgtgctaa	agtgccagcc	caaggkggtc	240
aaaagtccac	aaaactgcag	tctttgctgg	gatagtaagc	caagcagtgc	ctggacagca	300
gagttctttt	cttggcaac	agataaccag	acaggactct	aatcgtgctc	ttattcaaca	360
ttcttctgtc	tctgcctaga	ctgaaataaa	aagccaatct	ctctcggtggc	acagggaagg	420
agatacaagc	tcgtttacat	gtgatagatc	taacaaaggc	atctaccgaa	gtctggctg	480
gatagacggc	acaggagct	cttaggtcag	cgctgctggt	tggaggacat	tcctgagtcc	540
agctttgcag	cctttgtca	acagtaacttt	cccc			574

<210> 357
<211> 393
<212> DNA
<213> Homo sapien

<400> 357	
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aagccacaac caaracttga ttttatcaac aaaaacccct aaatataaaac ggsaaaaaaag	180
atagatataa ttattccagt ttttttaaaa cttaaaarat attccatgc cgaattaara	240
araarataag tgatatatgg aaagaaggc atccaaggcac actaaaraaaa cctgaggkaa	300
gcataatctg tacaaaatta aactgtcctt tttggcattt taacaaattt gcaacgktct	360
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<210> 358
<211> 630
<212> DNA
<213> Homo sapien

<400> 358	
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gcatagagta gggaaagctaa tccagcacag ggaggtcaca gagacatccc taaggaagtg	180
gagtttaaac tgagagaagc aagtgtttaa actgaaggat gtgttgaaga agaagggaga	240
gtagaacaat ttggcagag ggaaccttta agaccctaag gtggaaaggt tcaaagaact	300
gaaagagagc tagaacagct ggagccgttc tccgggttaa agaggagtc aagagataag	360
attaaagatg tgaagattaa gatcttggtg gcattcaggat attggcactt ctacaagaaa	420
tcactgaagg gagtaatgtg acattactt tcacttcagg atggccatcc taactccagg	480
gggttagactg gacttagtaa gactggaggc agtagaccc cttctaaggc ctgcgatagt	540
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caagccagag gtcctccac aacaaccagt	630

<210> 359
<211> 620
<212> DNA
<213> Homo sapien

<400> 359	
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ctcaccagaa gaataaaatg ctctgccagt tattaaagga ttactgtgg tgaattaaat	180
atggcattcc ccaaggaaa tagagagatt cttctggatt atgttcaata tttatccac	240
aggattaact gttttagaa cagatataaa gcttcgccac ggaagagatg gacaaagcac	300
aaagacaaca tgataccctt ggaagcaaca ctacccttcc aggcataaaa tttggagaaa	360
tgcaacatta tgcttcatga ataatatgta gaaagaaggt ctgatgaaaa tgacatcctt	420
aatgttaagat aactttataa gaattctggg tcaaataaaa ttcttgaag aaaacatcca	480
aatgtcattg acttatcaa tactatctt gcatataacc tatgaaggca aaactaaaca	540
aacaaaaaagc tcacacccaa caaaaccatc aacttatttt gtattctata acatacgaga	600
ctgtaaagat gtgacagtgt	620

<210> 360
 <211> 431
 <212> DNA
 <213> Homo sapien

<400> 360
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 tactcatcat tttggccag cagttgttg atcaccaaac atcatgccag aataactcagc 180
 aaaccttctt agctcttgag aagtcaaaat ccgggggaaat ttattcctgg caattttaat 240
 tggactcctt atgtgagagc agcggttacc cagctgggtt ggtggagcga acccgtaact 300
 agtggacatg cagttggcaga gctcctggta accaccta ggaatacaca ggcacatgtg 360
 tcatgtatcaag cgtgacacct gtagcactca aatttgttctt gttttgtct ttcgggtgtgt 420
 agattcttag t 431

<210> 361
 <211> 351
 <212> DNA
 <213> Homo sapien

<400> 361
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 ttgggtcctt tggctcttg ccaagttcc cagccactcg agggagaaat atcgggaggt 180
 ttgacttctt ccggggcttt cccgagggtt tcaccgtgag ccctgcggcc ctcagggtctg 240
 caatccttggaa ttcaatgtct gaaacctcgc tctctgcctg ctggacttctt gaggccgtca 300
 ctggccactctt gtcctccagc tctgacagct cctcatctgt ggtcctgtt g 351

<210> 362
 <211> 463
 <212> DNA
 <213> Homo sapien

<400> 362
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 ccccggtcac agaaatgacc aggttgggtt tttcaggtt ccagtgtt gtcagcagct 180
 cgtaaaggat ttccgcgtcc gtgtcgcagg acagacgtat atacttccct ttcttccccca 240
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 agttccattt ctcactttgg ttgatctggg tgcctccat gtgctggctc tggcatagc 360
 cacacttgca cacattctcc ctgataagca cgatgggtgtt gacaggaagg aaggatttca 420
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<210> 363
 <211> 653
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(653)

<223> n = A,T,C or G

<400> 363

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tgggaggcac tacgcaagat gggactgcgt cctgggggtga gacatcctct ccttggagat		180
ctaacgaaac ttctcaccta tgagttgtaa agcagaaaata cctgnactac agacgagtgc		240
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attttggaga tccntggtcc agaattccat ttaccttctg ggccagatac caccagaatg		600
cccgctccag attccctcag acctttgccg gtcccaattat tggcstggt ggt		653

<210> 364

<211> 401

<212> DNA

<213> Homo sapien

<400> 364

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aaaacaaggt ggatagatct agaattgtaa cattttaaga aaaccatagc atttgacaga		180
tgagaaaagct caattataga tgcaaagttt taactaaact actatagtag taaagaaaata		240
catttcacac ccttcataata aattcactat ctggcttga ggcactccat aaaatgtatc		300
acgtgcatacg taaatctta tatttgctat ggcgttgac tagaggactt ggactgcaac		360
aagtggatgc gcggaaaatg aaatcttctt caatagccca g		401

<210> 365

<211> 356

<212> DNA

<213> Homo sapien

<400> 365

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taccagagca tcaagtctct gcagcagtc attcttgggt aaagaaaatga ctccacaaa		180
ctctccatcc cctggcttgc gttcggccct tgcgtttcg gcatcatctc cgtaatgggt		240
gactgtcactg atgtgtatag tacagtttgc caagcctggg tccatacaga ccgctggaga		300
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<210> 366

<211> 1851

<212> DNA

<213> Homo sapien

<400> 366

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cttccgtgtt cttcatttctt cttcaatagc cataaaatctt ctagctctgg ctggctgttt		120
tcacttcctt taaggcttttgc tgactcttcc tctgatgtca gtttaagtc ttgttctgga		180

ttgctgtttt cagaagagat ttttaacatc tgttttctt ttagtcaga aagtaactgg	240
caaattacat gatgatgact agaaacagca tactctctgg ccgtcttcc agatcttgag	300
aagatacatc aacatttgc tcaagtagag ggctgactat acttgctgat ccacaacata	360
cagcaagtat gagagcagtt ctccatatc tattcagcgc atttaaattc gctttttct	420
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gcacgagtt tactacttct gaattccat tggcagaggc cagatgtaga gcagtccctct	780
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ctttccca ttttagtatta ttgtggctgtt gggcttgc taggtgtttt ttattacttt	1800
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<210> 367

<211> 668

<212> DNA

<213> Homo sapien

<400> 367

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accrtataag agcagtgcctt tggccatcaa ttatcttcc attrtagaca gcrtagtgya	180
gagtggattt tccatactca tctggatattt ttggatcgtt gccatgttcc agcaacattt	240
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agaaaactca tttttatgcc atgtatttgc atcaaaccctt cctcatgtt atatagttgg	420
ctactgcata ctttgcattt agctgttcc ttggatcgtt caaggacatt aagttgacat	480
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gcagtccat gagagtgaga agacttttta gaaattgtt gtcacttgc tacagccata	600
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<210> 368

<211> 1512

<212> DNA

<213> Homo sapien

<400> 368

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cactgctcc	cctgctgcag	ggggagttggc	aagagcaacg	tgggcgttc	tggagaccac	480
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gaagtagtaa	aactcstgct	ggacagacga	tgtcaactta	atgtccttga	caacaaaaag	840
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gaacatggca	ctgatccaa	tattccagat	gagtatggaa	ataccactct	ractaygt	960
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actccaagaa	aagttaaaca	tgttcagtg	aatagagatc	ctgctcctt	ggcaagttcc	1440
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<210> 369

<211> 1853

<212> DNA

<213> Homo sapien

<400> 369

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<210> 370
<211> 2184
<212> DNA
<213> Homo sapien

<400> 370		
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ccatcgtgca tgcacatcttccat	tttcttcctc	780
ggcaagagca acgtgggcac ttctggagac	cacaacgact	840
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acgtggtcgc ttggggagac tacgatgaca	gccccttcat	960
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ctctacatctt ggcctctgca	aatggaaatt	1140
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aagcactgct cttatacggt	gctgatatcg	1440
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	atccagaaca	

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<210> 371
<211> 1855
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(1855)
<223> n = A,T,C or G
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<400> 371
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<212> DNA	
<213> Homo sapien	
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<210> 374
 <211> 2000
 <212> DNA
 <213> Homo sapien

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<210> 375
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 <212> DNA
 <213> Homo sapien

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<210> 376

<211> 329

<212> PRT

<213> Homo sapien

<400> 376

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      20          25          30
Glu Tyr Thr Ile Val His Ala Ser Phe Ile Ser Cys Ile Ser Ser Ser
      35          40          45
Leu Asp Gly Gln Gly Glu Arg Gln Glu Gln Arg Gly His Phe Trp Arg
      50          55          60
Pro Gln Arg Leu Leu Cys Glu Asp Ala Trp Glu Gln Glu Val Gln Val
      65          70          75          80
Val Leu Pro Leu Leu Pro Leu Leu Gln Gly Ser Gly Lys Ser Asn Val

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Val Ala Trp Gly Asp Tyr Asp Asp Ser Ala Phe Met Asp Pro Arg Tyr			
100	105	110	
His Val His Gly Glu Asp Leu Asp Lys Leu His Arg Ala Ala Trp Trp			
115	120	125	
Gly Lys Val Pro Arg Lys Asp Leu Ile Val Met Leu Arg Asp Thr Asp			
130	135	140	
Val Asn Lys Arg Asp Lys Gln Lys Arg Thr Ala Leu His Leu Ala Ser			
145	150	155	160
Ala Asn Gly Asn Ser Glu Val Val Lys Leu Val Leu Asp Arg Arg Cys			
165	170	175	
Gln Leu Asn Val Leu Asp Asn Lys Lys Arg Thr Ala Leu Thr Lys Ala			
180	185	190	
Val Gln Cys Gln Glu Asp Glu Cys Ala Leu Met Leu Leu Glu His Gly			
195	200	205	
Thr Asp Pro Asn Ile Pro Asp Glu Tyr Gly Asn Thr Thr Leu His Tyr			
210	215	220	
Ala Val Tyr Asn Glu Asp Lys Leu Met Ala Lys Ala Leu Leu Leu Tyr			
225	230	235	240
Gly Ala Asp Ile Glu Ser Lys Asn Lys His Gly Leu Thr Pro Leu Leu			
245	250	255	
Leu Gly Ile His Glu Gln Lys Gln Gln Val Val Lys Phe Leu Ile Lys			
260	265	270	
Lys Lys Ala Asn Leu Asn Ala Leu Asp Arg Tyr Gly Arg Thr Ala Leu			
275	280	285	
Ile Leu Ala Val Cys Cys Gly Ser Ala Ser Ile Val Ser Pro Leu Leu			
290	295	300	
Glu Gln Asn Val Asp Val Ser Ser Gln Asp Leu Glu Arg Arg Pro Glu			
305	310	315	320
Ser Met Leu Phe Leu Val Ile Ile Met			
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<210> 377
<211> 148
<212> PRT
<213> Homo sapien

<220>
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Asp Leu Ile Val Met Leu Arg Asp Thr Asp Val Asn Lys Xaa Asp Lys			
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Gln Lys Arg Thr Ala Leu His Leu Ala Ser Ala Asn Gly Asn Ser Glu			
50	55	60	

Val Val Lys Leu Xaa Leu Asp Arg Arg Cys Gln Leu Asn Val Leu Asp
 65 70 75 80
 Asn Lys Lys Arg Thr Ala Leu Xaa Lys Ala Val Gln Cys Gln Glu Asp
 85 90 95
 Glu Cys Ala Leu Met Leu Leu Glu His Gly Thr Asp Pro Asn Ile Pro
 100 105 110
 Asp Glu Tyr Gly Asn Thr Thr Leu His Tyr Ala Xaa Tyr Asn Glu Asp
 115 120 125
 Lys Leu Met Ala Lys Ala Leu Leu Leu Tyr Gly Ala Asp Ile Glu Ser
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 Lys Asn Lys Val
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<210> 378
 <211> 1719
 <212> PRT
 <213> Homo sapien

<400> 378

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His	Asp	Asp	Ser	Ala	Met	Lys	Thr	Leu	Arg	Ser	Lys	Met	Gly	Lys	Trp
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Cys	Arg	His	Cys	Phe	Pro	Cys	Cys	Arg	Gly	Ser	Gly	Lys	Ser	Asn	Val
							65				70			75	
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Lys	Met	Gly	Lys	Trp	Cys	Cys	His	Cys	Phe	Pro	Cys	Cys	Arg	Gly	Ser
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							180				185			190	
Leu	Asp	Arg	Arg	Cys	Gln	Leu	Asn	Val	Leu	Asp	Asn	Lys	Lys	Arg	Thr
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Ala	Leu	Ile	Lys	Ala	Val	Gln	Cys	Gln	Glu	Asp	Glu	Cys	Ala	Leu	Met
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Leu	Leu	Glu	His	Gly	Thr	Asp	Pro	Asn	Ile	Pro	Asp	Glu	Tyr	Gly	Asn
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Thr	Thr	Leu	His	Tyr	Ala	Ile	Tyr	Asn	Glu	Asp	Lys	Leu	Met	Ala	Lys
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Ala Leu Leu Leu Tyr Gly Ala Asp Ile Glu Ser Lys Asn Lys His Gly
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 Lys Phe Leu Ile Lys Lys Ala Asn Leu Asn Ala Leu Asp Arg Tyr
 290 295 300
 Gly Arg Thr Ala Leu Ile Leu Ala Val Cys Cys Gly Ser Ala Ser Ile
 305 310 315 320
 Val Ser Leu Leu Leu Glu Gln Asn Ile Asp Val Ser Ser Gln Asp Leu
 325 330 335
 Ser Gly Gln Thr Ala Arg Glu Tyr Ala Val Ser Ser His His His Val
 340 345 350
 Ile Cys Gln Leu Leu Ser Asp Tyr Lys Glu Lys Gln Met Leu Lys Ile
 355 360 365
 Ser Ser Glu Asn Ser Asn Pro Glu Asn Val Ser Arg Thr Arg Asn Lys
 370 375 380
 Pro Arg Thr His Met Val Val Glu Val Asp Ser Met Pro Ala Ala Ser
 385 390 395 400
 Ser Val Lys Lys Pro Phe Gly Leu Arg Ser Lys Met Gly Lys Trp Cys
 405 410 415
 Cys Arg Cys Phe Pro Cys Cys Arg Glu Ser Gly Lys Ser Asn Val Gly
 420 425 430
 Thr Ser Gly Asp His Asp Asp Ser Ala Met Lys Thr Leu Arg Ser Lys
 435 440 445
 Met Gly Lys Trp Cys Arg His Cys Phe Pro Cys Cys Arg Gly Ser Gly
 450 455 460
 Lys Ser Asn Val Gly Ala Ser Gly Asp His Asp Asp Ser Ala Met Lys
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 Thr Leu Arg Asn Lys Met Gly Lys Trp Cys Cys His Cys Phe Pro Cys
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 Cys Arg Gly Ser Gly Lys Ser Lys Val Gly Ala Trp Gly Asp Tyr Asp
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 Asp Ser Ala Phe Met Glu Pro Arg Tyr His Val Arg Gly Glu Asp Leu
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 Asp Lys Leu His Arg Ala Ala Trp Trp Gly Lys Val Pro Arg Lys Asp
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 545 550 555 560
 Lys Arg Thr Ala Leu His Leu Ala Ser Ala Asn Gly Asn Ser Glu Val
 565 570 575
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 Lys Lys Arg Thr Ala Leu Ile Lys Ala Val Gln Cys Gln Glu Asp Glu
 595 600 605
 Cys Ala Leu Met Leu Leu Glu His Gly Thr Asp Pro Asn Ile Pro Asp
 610 615 620
 Glu Tyr Gly Asn Thr Thr Leu His Tyr Ala Ile Tyr Asn Glu Asp Lys
 625 630 635 640
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 645 650 655
 Asn Lys His Gly Leu Thr Pro Leu Leu Leu Gly Val His Glu Gln Lys

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Gln Gln Val Val Lys Phe Leu Ile Lys Lys Lys Ala Asn Leu Asn Ala		
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Leu Asp Arg Tyr Gly Arg Thr Ala Leu Ile Leu Ala Val Cys Cys Gly		
690	695	700
Ser Ala Ser Ile Val Ser Leu Leu Leu Glu Gln Asn Ile Asp Val Ser		
705	710	715
Ser Gln Asp Leu Ser Gly Gln Thr Ala Arg Glu Tyr Ala Val Ser Ser		
725	730	735
His His His Val Ile Cys Gln Leu Leu Ser Asp Tyr Lys Glu Lys Gln		
740	745	750
Met Leu Lys Ile Ser Ser Glu Asn Ser Asn Pro Glu Gln Asp Leu Lys		
755	760	765
Leu Thr Ser Glu Glu Glu Ser Gln Arg Phe Lys Gly Ser Glu Asn Ser		
770	775	780
Gln Pro Glu Lys Met Ser Gln Glu Pro Glu Ile Asn Lys Asp Gly Asp		
785	790	795
Arg Glu Val Glu Glu Met Lys Lys His Glu Ser Asn Asn Val Gly		
805	810	815
Leu Leu Glu Asn Leu Thr Asn Gly Val Thr Ala Gly Asn Gly Asp Asn		
820	825	830
Gly Leu Ile Pro Gln Arg Lys Ser Arg Thr Pro Glu Asn Gln Gln Phe		
835	840	845
Pro Asp Asn Glu Ser Glu Glu Tyr His Arg Ile Cys Glu Leu Val Ser		
850	855	860
Asp Tyr Lys Glu Lys Gln Met Pro Lys Tyr Ser Ser Glu Asn Ser Asn		
865	870	875
Pro Glu Gln Asp Leu Lys Leu Thr Ser Glu Glu Glu Ser Gln Arg Leu		
885	890	895
Glu Gly Ser Glu Asn Gly Gln Pro Glu Leu Glu Asn Phe Met Ala Ile		
900	905	910
Glu Glu Met Lys His Gly Ser Thr His Val Gly Phe Pro Glu Asn		
915	920	925
Leu Thr Asn Gly Ala Thr Ala Gly Asn Gly Asp Asp Gly Leu Ile Pro		
930	935	940
Pro Arg Lys Ser Arg Thr Pro Glu Ser Gln Gln Phe Pro Asp Thr Glu		
945	950	955
Asn Glu Glu Tyr His Ser Asp Glu Gln Asn Asp Thr Gln Lys Gln Phe		
965	970	975
Cys Glu Glu Gln Asn Thr Gly Ile Leu His Asp Glu Ile Leu Ile His		
980	985	990
Glu Glu Lys Gln Ile Glu Val Val Glu Lys Met Asn Ser Glu Leu Ser		
995	1000	1005
Leu Ser Cys Lys Lys Glu Lys Asp Ile Leu His Glu Asn Ser Thr Leu		
1010	1015	1020
Arg Glu Glu Ile Ala Met Leu Arg Leu Glu Leu Asp Thr Met Lys His		
1025	1030	1035
Gln Ser Gln Leu Pro Arg Thr His Met Val Val Glu Val Asp Ser Met		
1045	1050	1055
Pro Ala Ala Ser Ser Val Lys Lys Pro Phe Gly Leu Arg Ser Lys Met		
1060	1065	1070

Gly Lys Trp Cys Cys Arg Cys Phe Pro Cys Cys Arg Glu Ser Gly Lys
 1075 1080 1085
 Ser Asn Val Gly Thr Ser Gly Asp His Asp Asp Ser Ala Met Lys Thr
 1090 1095 1100
 Leu Arg Ser Lys Met Gly Lys Trp Cys Arg His Cys Phe Pro Cys Cys
 1105 1110 1115 112
 Arg Gly Ser Gly Lys Ser Asn Val Gly Ala Ser Gly Asp His Asp Asp
 1125 1130 1135
 Ser Ala Met Lys Thr Leu Arg Asn Lys Met Gly Lys Trp Cys Cys His
 1140 1145 1150
 Cys Phe Pro Cys Cys Arg Gly Ser Gly Lys Ser Lys Val Gly Ala Trp
 1155 1160 1165
 Gly Asp Tyr Asp Asp Ser Ala Phe Met Glu Pro Arg Tyr His Val Arg
 1170 1175 1180
 Gly Glu Asp Leu Asp Lys Leu His Arg Ala Ala Trp Trp Gly Lys Val
 1185 1190 1195 120
 Pro Arg Lys Asp Leu Ile Val Met Leu Arg Asp Thr Asp Val Asn Lys
 1205 1210 1215
 Lys Asp Lys Gln Lys Arg Thr Ala Leu His Leu Ala Ser Ala Asn Gly
 1220 1225 1230
 Asn Ser Glu Val Val Lys Leu Leu Asp Arg Arg Cys Gln Leu Asn
 1235 1240 1245
 Val Leu Asp Asn Lys Lys Arg Thr Ala Leu Ile Lys Ala Val Gln Cys
 1250 1255 1260
 Gln Glu Asp Glu Cys Ala Leu Met Leu Leu Glu His Gly Thr Asp Pro
 1265 1270 1275 128
 Asn Ile Pro Asp Glu Tyr Gly Asn Thr Thr Leu His Tyr Ala Ile Tyr
 1285 1290 1295
 Asn Glu Asp Lys Leu Met Ala Lys Ala Leu Leu Leu Tyr Gly Ala Asp
 1300 1305 1310
 Ile Glu Ser Lys Asn Lys His Gly Leu Thr Pro Leu Leu Leu Gly Val
 1315 1320 1325
 His Glu Gln Lys Gln Gln Val Val Lys Phe Leu Ile Lys Lys Lys Ala
 1330 1335 1340
 Asn Leu Asn Ala Leu Asp Arg Tyr Gly Arg Thr Ala Leu Ile Leu Ala
 1345 1350 1355 136
 Val Cys Cys Gly Ser Ala Ser Ile Val Ser Leu Leu Leu Glu Gln Asn
 1365 1370 1375
 Ile Asp Val Ser Ser Gln Asp Leu Ser Gly Gln Thr Ala Arg Glu Tyr
 1380 1385 1390
 Ala Val Ser Ser His His Val Ile Cys Gln Leu Leu Ser Asp Tyr
 1395 1400 1405
 Lys Glu Lys Gln Met Leu Lys Ile Ser Ser Glu Asn Ser Asn Pro Glu
 1410 1415 1420
 Gln Asp Leu Lys Leu Thr Ser Glu Glu Ser Gln Arg Phe Lys Gly
 1425 1430 1435 144
 Ser Glu Asn Ser Gln Pro Glu Lys Met Ser Gln Glu Pro Glu Ile Asn
 1445 1450 1455
 Lys Asp Gly Asp Arg Glu Val Glu Glu Met Lys Lys His Glu Ser
 1460 1465 1470
 Asn Asn Val Gly Leu Leu Glu Asn Leu Thr Asn Gly Val Thr Ala Gly

1475	1480	1485
Asn Gly Asp Asn Gly Leu Ile Pro Gln Arg Lys Ser Arg Thr Pro Glu		
1490	1495	1500
Asn Gln Gln Phe Pro Asp Asn Glu Ser Glu Glu Tyr His Arg Ile Cys		
1505	1510	1515
Glu Leu Val Ser Asp Tyr Lys Glu Lys Gln Met Pro Lys Tyr Ser Ser		
1525	1530	1535
Glu Asn Ser Asn Pro Glu Gln Asp Leu Lys Leu Thr Ser Glu Glu Glu		
1540	1545	1550
Ser Gln Arg Leu Glu Gly Ser Glu Asn Gly Gln Pro Glu Lys Arg Ser		
1555	1560	1565
Gln Glu Pro Glu Ile Asn Lys Asp Gly Asp Arg Glu Leu Glu Asn Phe		
1570	1575	1580
Met Ala Ile Glu Glu Met Lys Lys His Gly Ser Thr His Val Gly Phe		
1585	1590	1595
Pro Glu Asn Leu Thr Asn Gly Ala Thr Ala Gly Asn Gly Asp Asp Gly		
1605	1610	1615
Leu Ile Pro Pro Arg Lys Ser Arg Thr Pro Glu Ser Gln Gln Phe Pro		
1620	1625	1630
Asp Thr Glu Asn Glu Glu Tyr His Ser Asp Glu Gln Asn Asp Thr Gln		
1635	1640	1645
Lys Gln Phe Cys Glu Glu Gln Asn Thr Gly Ile Leu His Asp Glu Ile		
1650	1655	1660
Leu Ile His Glu Glu Lys Gln Ile Glu Val Val Glu Lys Met Asn Ser		
1665	1670	1675
Glu Leu Ser Leu Ser Cys Lys Lys Glu Lys Asp Ile Leu His Glu Asn		
1685	1690	1695
Ser Thr Leu Arg Glu Glu Ile Ala Met Leu Arg Leu Glu Leu Asp Thr		
1700	1705	1710
Met Lys His Gln Ser Gln Leu		
1715		

<210> 379
 <211> 656
 <212> PRT
 <213> Homo sapien

<400> 379		
Met Val Val Glu Val Asp Ser Met Pro Ala Ala Ser Ser Val Lys Lys		
1	5	10
Pro Phe Gly Leu Arg Ser Lys Met Gly Lys Trp Cys Cys Arg Cys Phe		
20	25	30
Pro Cys Cys Arg Glu Ser Gly Lys Ser Asn Val Gly Thr Ser Gly Asp		
35	40	45
His Asp Asp Ser Ala Met Lys Thr Leu Arg Ser Lys Met Gly Lys Trp		
50	55	60
Cys Arg His Cys Phe Pro Cys Cys Arg Gly Ser Gly Lys Ser Asn Val		
65	70	75
Gly Ala Ser Gly Asp His Asp Asp Ser Ala Met Lys Thr Leu Arg Asn		
85	90	95
Lys Met Gly Lys Trp Cys Cys His Cys Phe Pro Cys Cys Arg Gly Ser		

100	105	110
Gly Lys Ser Lys Val Gly Ala Trp	Gly Asp Tyr Asp Asp Ser Ala Phe	
115	120	125
Met Glu Pro Arg Tyr His Val Arg	Gly Glu Asp Leu Asp Lys Leu His	
130	135	140
Arg Ala Ala Trp Trp Gly Lys Val Pro Arg	Lys Asp Leu Ile Val Met	
145	150	155
Leu Arg Asp Thr Asp Val Asn Lys Lys	Asp Lys Gln Lys Arg Thr Ala	
165	170	175
Leu His Leu Ala Ser Ala Asn Gly Asn	Ser Glu Val Val Lys Leu Leu	
180	185	190
Leu Asp Arg Arg Cys Gln Leu Asn Val	Leu Asp Asn Lys Lys Arg Thr	
195	200	205
Ala Leu Ile Lys Ala Val Gln Cys Gln	Glu Asp Glu Cys Ala Leu Met	
210	215	220
Leu Leu Glu His Gly Thr Asp Pro Asn Ile	Pro Asp Glu Tyr Gly Asn	
225	230	235
Thr Thr Leu His Tyr Ala Ile Tyr Asn	Glu Asp Lys Leu Met Ala Lys	
245	250	255
Ala Leu Leu Leu Tyr Gly Ala Asp Ile	Glu Ser Lys Asn Lys His Gly	
260	265	270
Leu Thr Pro Leu Leu Leu Gly Val His	Glu Gln Lys Gln Gln Val Val	
275	280	285
Lys Phe Leu Ile Lys Lys Ala Asn Leu Asn	Ala Leu Asp Arg Tyr	
290	295	300
Gly Arg Thr Ala Leu Ile Leu Ala Val	Cys Cys Gly Ser Ala Ser Ile	
305	310	315
Val Ser Leu Leu Leu Glu Gln Asn Ile	Asp Val Ser Ser Gln Asp Leu	
325	330	335
Ser Gly Gln Thr Ala Arg Glu Tyr Ala	Val Ser Ser His His His Val	
340	345	350
Ile Cys Gln Leu Leu Ser Asp Tyr	Lys Glu Lys Gln Met Leu Lys Ile	
355	360	365
Ser Ser Glu Asn Ser Asn Pro Glu Gln	Asp Leu Lys Leu Thr Ser Glu	
370	375	380
Glu Glu Ser Gln Arg Phe Lys Gly Ser	Glu Asn Ser Gln Pro Glu Lys	
385	390	395
Met Ser Gln Glu Pro Glu Ile Asn Lys	Asp Gly Asp Arg Glu Val Glu	
405	410	415
Glu Glu Met Lys Lys His Glu Ser Asn	Asn Val Gly Leu Leu Glu Asn	
420	425	430
Leu Thr Asn Gly Val Thr Ala Gly Asn	Gly Asp Asn Gly Leu Ile Pro	
435	440	445
Gln Arg Lys Ser Arg Thr Pro Glu Asn	Gln Gln Phe Pro Asp Asn Glu	
450	455	460
Ser Glu Glu Tyr His Arg Ile Cys Glu	Leu Val Ser Asp Tyr Lys Glu	
465	470	475
Lys Gln Met Pro Lys Tyr Ser Ser Glu	Asn Ser Asn Pro Glu Gln Asp	
485	490	495
Leu Lys Leu Thr Ser Glu Glu Glu Ser	Gln Arg Leu Glu Gly Ser Glu	
500	505	510

Asn Gly Gln Pro Glu Leu Glu Asn Phe Met Ala Ile Glu Glu Met Lys
 515 520 525
 Lys His Gly Ser Thr His Val Gly Phe Pro Glu Asn Leu Thr Asn Gly
 530 535 540
 Ala Thr Ala Gly Asn Gly Asp Asp Gly Leu Ile Pro Pro Arg Lys Ser
 545 550 555 560
 Arg Thr Pro Glu Ser Gln Gln Phe Pro Asp Thr Glu Asn Glu Glu Tyr
 565 570 575
 His Ser Asp Glu Gln Asn Asp Thr Gln Lys Gln Phe Cys Glu Glu Gln
 580 585 590
 Asn Thr Gly Ile Leu His Asp Glu Ile Leu Ile His Glu Glu Lys Gln
 595 600 605
 Ile Glu Val Val Glu Lys Met Asn Ser Glu Leu Ser Leu Ser Cys Lys
 610 615 620
 Lys Glu Lys Asp Ile Leu His Glu Asn Ser Thr Leu Arg Glu Glu Ile
 625 630 635 640
 Ala Met Leu Arg Leu Glu Leu Asp Thr Met Lys His Gln Ser Gln Leu
 645 650 655

<210> 380
 <211> 671
 <212> PRT
 <213> Homo sapien

<400> 380
 Met Val Val Glu Val Asp Ser Met Pro Ala Ala Ser Ser Val Lys Lys
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 Pro Phe Gly Leu Arg Ser Lys Met Gly Lys Trp Cys Cys Arg Cys Phe
 20 25 30
 Pro Cys Cys Arg Glu Ser Gly Lys Ser Asn Val Gly Thr Ser Gly Asp
 35 40 45
 His Asp Asp Ser Ala Met Lys Thr Leu Arg Ser Lys Met Gly Lys Trp
 50 55 60
 Cys Arg His Cys Phe Pro Cys Cys Arg Gly Ser Gly Lys Ser Asn Val
 65 70 75 80
 Gly Ala Ser Gly Asp His Asp Asp Ser Ala Met Lys Thr Leu Arg Asn
 85 90 95
 Lys Met Gly Lys Trp Cys Cys His Cys Phe Pro Cys Cys Arg Gly Ser
 100 105 110
 Gly Lys Ser Lys Val Gly Ala Trp Gly Asp Tyr Asp Asp Ser Ala Phe
 115 120 125
 Met Glu Pro Arg Tyr His Val Arg Gly Glu Asp Leu Asp Lys Leu His
 130 135 140
 Arg Ala Ala Trp Trp Gly Lys Val Pro Arg Lys Asp Leu Ile Val Met
 145 150 155 160
 Leu Arg Asp Thr Asp Val Asn Lys Lys Asp Lys Gln Lys Arg Thr Ala
 165 170 175
 Leu His Leu Ala Ser Ala Asn Gly Asn Ser Glu Val Val Lys Leu Leu
 180 185 190
 Leu Asp Arg Arg Cys Gln Leu Asn Val Leu Asp Asn Lys Lys Arg Thr
 195 200 205

Ala Leu Ile Lys Ala Val Gln Cys Gln Glu Asp Glu Cys Ala Leu Met
 210 215 220
 Leu Leu Glu His Gly Thr Asp Pro Asn Ile Pro Asp Glu Tyr Gly Asn
 225 230 235 240
 Thr Thr Leu His Tyr Ala Ile Tyr Asn Glu Asp Lys Leu Met Ala Lys
 245 250 255
 Ala Leu Leu Leu Tyr Gly Ala Asp Ile Glu Ser Lys Asn Lys His Gly
 260 265 270
 Leu Thr Pro Leu Leu Leu Gly Val His Glu Gln Lys Gln Gln Val Val
 275 280 285
 Lys Phe Leu Ile Lys Lys Ala Asn Leu Asn Ala Leu Asp Arg Tyr
 290 295 300
 Gly Arg Thr Ala Leu Ile Leu Ala Val Cys Cys Gly Ser Ala Ser Ile
 305 310 315 320
 Val Ser Leu Leu Leu Glu Gln Asn Ile Asp Val Ser Ser Gln Asp Leu
 325 330 335
 Ser Gly Gln Thr Ala Arg Glu Tyr Ala Val Ser Ser His His His Val
 340 345 350
 Ile Cys Gln Leu Leu Ser Asp Tyr Lys Glu Lys Gln Met Leu Lys Ile
 355 360 365
 Ser Ser Glu Asn Ser Asn Pro Glu Gln Asp Leu Lys Leu Thr Ser Glu
 370 375 380
 Glu Glu Ser Gln Arg Phe Lys Gly Ser Glu Asn Ser Gln Pro Glu Lys
 385 390 395 400
 Met Ser Gln Glu Pro Glu Ile Asn Lys Asp Gly Asp Arg Glu Val Glu
 405 410 415
 Glu Glu Met Lys Lys His Glu Ser Asn Asn Val Gly Leu Leu Glu Asn
 420 425 430
 Leu Thr Asn Gly Val Thr Ala Gly Asn Gly Asp Asn Gly Leu Ile Pro
 435 440 445
 Gln Arg Lys Ser Arg Thr Pro Glu Asn Gln Gln Phe Pro Asp Asn Glu
 450 455 460
 Ser Glu Glu Tyr His Arg Ile Cys Glu Leu Val Ser Asp Tyr Lys Glu
 465 470 475 480
 Lys Gln Met Pro Lys Tyr Ser Ser Glu Asn Ser Asn Pro Glu Gln Asp
 485 490 495
 Leu Lys Leu Thr Ser Glu Glu Ser Gln Arg Leu Glu Gly Ser Glu
 500 505 510
 Asn Gly Gln Pro Glu Lys Arg Ser Gln Glu Pro Glu Ile Asn Lys Asp
 515 520 525
 Gly Asp Arg Glu Leu Glu Asn Phe Met Ala Ile Glu Glu Met Lys Lys
 530 535 540
 His Gly Ser Thr His Val Gly Phe Pro Glu Asn Leu Thr Asn Gly Ala
 545 550 555 560
 Thr Ala Gly Asn Gly Asp Asp Gly Leu Ile Pro Pro Arg Lys Ser Arg
 565 570 575
 Thr Pro Glu Ser Gln Gln Phe Pro Asp Thr Glu Asn Glu Glu Tyr His
 580 585 590
 Ser Asp Glu Gln Asn Asp Thr Gln Lys Gln Phe Cys Glu Glu Gln Asn
 595 600 605
 Thr Gly Ile Leu His Asp Glu Ile Leu Ile His Glu Glu Lys Gln Ile

610	615	620
Glu Val Val Glu Lys Met Asn Ser Glu Leu Ser	Lys Cys Lys Lys	
625	630	635
Glu Lys Asp Ile Leu His Glu Asn Ser Thr Leu Arg	Glu Ile Ala	640
645	650	655
Met Leu Arg Leu Glu Leu Asp Thr Met Lys His Gln	Ser Gln Leu	
660	665	670

<210> 381

<211> 251

<212> DNA

<213> Homo sapien

<400> 381

ggagaagcgt ctgctgggc aggaagggt ttccctgcc	tctcacctgt ccctcaccaa	60
ggtaacatgc ttccoctaa ggtatccaa cccaggggcc	tcaccatgac ctctgagggg	120
ccaatatccc aggagaagca ttggggagtt gggggcaggt	gaaggaccca ggactcacac	180
atcctgggcc tccaaaggcag aggagagggt cctaagaag	gtcaggagga aaatccgtaa	240
caaggcgtca g		251

<210> 382

<211> 3279

<212> DNA

<213> Homo sapiens

<400> 382

cttcctgcag cccccatgct ggtgagggc acggcagga acagtggacc	caacatggaa	60
atgctggagg gtgtcaggaa gtgatcgggc tctggggcag ggaggagggg	tggggagtgt	120
cactgggagg ggacatcctg cagaaggtag gagtgagcaa acaccgcgt	caggggaggg	180
gagagccctg cggcacctgg gggagcagag ggagcagcac ctgcccaggg	ctgggaggag	240
gggcctggag ggcgtgagga ggagcgaggg ggctgcattt ctggagtgag	ggatcagggg	300
caggcgcgca gatggcctca cacaggaaag agagggcccc tcctgcaggg	cctcacctgg	360
gccacaggag gacactgctt ttcctctgag gagtcaggag ctgtggatgg	tgctggacag	420
aagaaggaca gggcctggct caggtgtcca gaggtgtcg ctggcttccc	tttggatca	480
gactgcaggg agggaggcg gcagggttgt gggggagtg acgtgagga	tgacactgggg	540
gtggctccag gccttgcctt tgcctggcc ctcacccagc ctcctcaca	gtctcctggc	600
cctcagtctc tccccctccac tccatcctcc atctggctc agtgggtcat	tctgatca	660
gaactgacca taccacccc tgcccacggc cttccatggc tccccatgc	cctggagagg	720
ggacatctag tcagagagta gtcctgaaga ggtggctct gcgtatgtcc	tgtggggca	780
gcacccctgca gatggtccc gcccctatcc tgctgacctg tctgcaggaa	ctgtcctcct	840
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gagccttggt ccctctgtt gactccctgc ccattatttt gtgggagtg	gttctggaga	960
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ttacccttag ggtgattctg ggggtccact tgtctgtaat ggtgtgc	aaggatcac	1140
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 cgctcagattt gatgatttcc tagcaggact tacagaaata aagagctatc atgctgttgt 1920
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 aagccccctt ggggatttgg tttggcttgg tgatcagggtg gtctatgggg ctatccctac 2700
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 ggcaagattt tgtggcactc ctggttacag atactggggc agcaaataaa actgaatctt 3240
 gttttcagac cttaaaaaaaaaaaaaaa aaaagtttt 3279

<210> 383

<211> 155

<212> PRT

<213> Homo sapiens

<400> 383

Met	Ala	Gly	Val	Arg	Asp	Gln	Gly	Gln	Gly	Ala	Arg	Trp	Pro	His	Thr

5

10

15

Gly	Lys	Arg	Gly	Pro	Leu	Leu	Gln	Gly	Leu	Thr	Trp	Ala	Thr	Gly	Gly

20

25

30

His	Cys	Phe	Ser	Ser	Glu	Glu	Ser	Gly	Ala	Val	Asp	Gly	Ala	Gly	Gln

35

40

45

Lys	Lys	Asp	Arg	Ala	Trp	Leu	Arg	Cys	Pro	Glu	Ala	Val	Ala	Gly	Phe

50

55

60

Pro	Leu	Gly	Ser	Asp	Cys	Arg	Glu	Gly	Gly	Arg	Gln	Gly	Cys	Gly	Gly

65

70

75

80

Ser Asp Asp Glu Asp Asp Leu Gly Val Ala Pro Gly Leu Ala Pro Ala
 85 90 95

Trp Ala Leu Thr Gln Pro Pro Ser Gln Ser Pro Gly Pro Gln Ser Leu
 100 105 110

Pro Ser Thr Pro Ser Ser Ile Trp Pro Gln Trp Val Ile Leu Ile Thr
 115 120 125

Glu Leu Thr Ile Pro Ser Pro Ala His Gly Pro Pro Trp Leu Pro Asn
 130 135 140

Ala Leu Glu Arg Gly His Leu Val Arg Glu
 145 150

<210> 384

<211> 557

<212> DNA

<213> Homo sapiens

<400> 384

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 ggggaagggtt ccctttgca ttgccaagtg ccataaccat gagcactact ctaccatgg 180
 tctgcctcct ggccaaggcag gctggtttc aagaatgaaa tgaatgattc tacagctagg 240
 acttaacctt gaaatggaaa gtcttgcaat cccatttgca ggatccgtct gtgcacatgc 300
 ctctgttagag agcagcattc ccagggacct tggaaacagt tggcactgta agtgcttgc 360
 tcccccaagac acatcctaaa aggtgttgc atggtaaaaa cgtcttcctt ctttattgcc 420
 ctttcttatt tatgtgaaca actgtttgtc tttttttgtt tcttttttaa actgtaaagt 480
 tcaattgtga aatgaatat catgcaaata aattatgcga ttttttttc aaagtaaaaa 540
 aaaaaaaaaa aaaaaaaaaa 557

<210> 385

<211> 337

<212> DNA

<213> Homo sapiens

<400> 385

tccccaggtg atgtgcgagg gaagacacat ttactatcct tggatgggct gattccttta 60
 gtttctctag cagcagatgg gtagggagga agtgacccaa gtgggtgact cctatgtgca 120
 tctcaaaagcc atctgctgtc ttcgagtacg gacacatcat cactcctgca ttgttgcata 180
 aaacgtggag gtgctttcc tcagctaaga agcccttagc aaaagctcga atagacttag 240
 tatcagacag gtccagtttc cgcaccaaca cctgctgggt ccctgtcgtg gtctggatct 300
 ctttggccac caattcccccc tttccacat cccggca 337

<210> 386

<211> 300

<212> DNA

<213> Homo sapiens

<400> 386

gggcccgtca ccggccccagg ccccgctcg cgagtcctcc tccccgggtg cctgcccgc 60
 gcccgcctcg cccagagggt gggcgcgggg ctgcctctac cggctggcgg ctgttaactca 120
 gcgacaccttg cccgaaggct ctagcaagga cccaccgacc ccagccgccc cggcggcggc 180
 gcggactttg cccggtgtgt ggggcgagc ggactgcgtg tccgcggacg ggcagcgaag 240
 atgttagcct tcgctgccag gaccgtggac cgatcccagg gctgtgggt aacccagcc 300

<210> 387

<211> 537

<212> DNA

<213> Homo sapiens

<400> 387

gggccgagtc gggcaccaag ggactcttg caggcttct tcctcgatc atcaaggctg 60
 cccctctcg tgccatcatg atcagcacct atgagtccgg caaaagcttc ttccagaggc 120
 tgaaccagga ccggcttctg ggcggctgaa aggggcaagg aggcaaggac cccgtcttc 180
 ccacggatgg ggagaggggca ggaggagacc cagccaagtg cctttcttc agcactgagg 240
 gagggggctt gtttcccttc cttcccgccg acaagctcca gggcaggcgt gtccctctgg 300
 gcggcccagc acttcctcag acacaacttc ttccgtctgc tccagtcgtg gggatcatca 360
 cttacccacc ccccaagttc aagaccaaattt cttccagctg ccccttcgt gtttccctgt 420
 gtttgctgta gctgggcatg tctccaggaa ccaagaagcc ctcagcctgg ttagtctcc 480
 ctgacccttg ttaattcctt aagtctaaatg atgatgaact taaaaaaaaaaaaaaa 537

<210> 388

<211> 520

<212> DNA

<213> Homo sapiens

<400> 388

aggataatt ttaaacaat caaatgaaaa aaacaaacaa aaaaaaaaaagg aaatgtcatg 60
 tgaggttaaa ccagtttgc ttcccttaat gtggaaaaag taagaggact actcagcact 120
 gtttgaagat tgcctcttc acagttctg agaattgtgt tatttcactt gccaaatgaa 180
 gacccccc cccaaacatgc cccagccac ccctaagcat ggtccctgtt caccaggca 240
 ccaggaaact gctacttgc gacccatcca gagaccagga gggtttgcgtt agctcacagg 300
 acttccccca ccccaagaaga ttagcatccc atactagact cataactcaac tcaacttaggc 360
 tcataactcaa ttgatggta ttagacaatt ccatttctt ctggtttata taaacagaaa 420
 atcttccttc ttctcattac cagtaaaggc tcttgcgttcc tttctgttgg aatgatttct 480
 atgaacttgtt cttatattaa tggtgggttt ttttctgtt 520

<210> 389

<211> 365

<212> DNA

<213> Homo sapiens

<400> 389

cgttccccca gtttgacaga aggaaaggcg gagcttatttcc aaagtctaga gggagtggag 60
 gagtttggc tggatttcag atctgcctgg ttccagccgc agtgtgcctt ctgtcccccc 120
 aacgactttc caaataatct caccagcgcc ttccagctca ggcgtccctag aagcgtcttg 180
 aacgcctatgg ccagctgtct ttgtgttccc tctcaccgc ctgtccctac agctgagact 240
 cccagggaaac cttcagacta cttccctctg cttcagccaa gggggcgatgc ccacatttc 300

tgagggtcag tggaagaacc tagactccca ttgcttagagg tagaaagggg aagggtgctg 360
gggag 365

<210> 390

<211> 221

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(221)

<223> n = A,T,C or G

<400> 390

tgcctctcca tcctggcccc gacttctctg tcagaaaagt ggggatggac cccatctgca 60
tacacggntt ctcatgggtg tggAACATCT ctgcttgcgg tttcaggaag gcctctggct 120
gctctangag tctgancnga ntctgtgccccc cantntgaca naaggaaagg cgagcttat 180
tcaaagtcta gaggagtggtgg aggagttaa gctggatttc a 221

<210> 391

<211> 325

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(325)

<223> n = A,T,C or G

<400> 391

tggagcaggccc cccgaggcct ccctagagcc tggggccgac tctgtgnca tgcangctt 60
ctctcgccccc cagcctggag ctgctcctgg catctaccaa caatcagnncg agggagcag 120
tagccaggccc actgctgcca acagccagtc cnatnacccat catgtgnaccc ggtgngctct 180
naantngat ntccanagcc ctaccatn tagtctgct ctcccacccgg ntaccagccc 240
caactgcccag gaatcctaca gccagtaccc tgtcccgacg tctctaccta ccagtacgat 300
gagacctcccg gctactacta tgacc 325

<210> 392

<211> 277

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(277)

<223> n = A,T,C or G

<400> 392

atattgtta actccttcct ttataatctt taacatttc atggngaaag gttcacatct 60
agtctcactt nggcnagnn ctcctacttg agtctcttcc ccggcctgnn ccagtnnn 120
antaccanga accgnatgn cttaanaacn ncctggtttn tgggttnntc aatgactgca 180

tgcagtgcac caccctgtcc actacgtat gctgtaggat taaaagtctca cagtgccgg 240
 ctgaggatac agcgccgcgt cctgtgttc tgggaa 277

<210> 393

<211> 566

<212> DNA

<213> Homo sapiens

<400> 393

actagtccag tgtggtgaa ttgcggccg cgtcgacgga caggtcagct gtctggctca 60
 gtgatctaca ttctgaagtt gtctgaaaat gtcttcatga ttaaattcag cctaaacgtt 120
 ttgccggaa cactgcagag acaatgctgt gagttccaa ccttagccca tctgcggca 180
 gagaaggctc agtttgcctca tcagcattat catgatatca ggactggta cttggtaag 240
 gaggggtcta ggagatctgt ccctttaga gacacccat ttataatgaa gtatttggaa 300
 ggggtgtttt caaaaatgaa aatgtcctgt attccgatga tcatcctgtt aacattttat 360
 catttattaa tcatcccgc ctgtgtctat tattatattc atatctcac gctggaaact 420
 ttctgcctca atgtttactg tgcctttgtt tttgttagtt tgggtttttt aaaaaaaaaa 480
 cattctctgc ctgagttta attttgtcc aaagttattt taatctatac aattaaaagc 540
 tttgcctat caaaaaaaaaa aaaaaaa 566

<210> 394

<211> 384

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(384)

<223> n = A,T,C or G

<400> 394

gaacatacat gtcccgac ctgagctgca gtctgacatc atcgccatca cgggcctcgc 60
 tgcaaattng gaccggcca aggctggact gctggagcgt gtgaaggagc tacaggccna 120
 gcaggaggac cgggcttaa ggagtttaa gctgagtgtc actgttagacc ccaaataccca 180
 tcccaagatt atcgggagaa agggggcagt aattacccaa atccgggtgg agcatgacgt 240
 gaacatccag tttcctgata aggacgtatgg gaaccagccc caggacccaa ttaccatcac 300
 agggtaacgaa aagaacacag aagctgccag ggatgctata ctgagaattt tgggtgaact 360
 tgagcagatg gttctgagg acgt 384

<210> 395

<211> 399

<212> DNA

<213> Homo sapiens

<400> 395

gcaaaaactg tgtgacctca ataagacctc gcagatccaa ggtcaagtat cagaagtgc 60
 tctgacctg gactccaaga cctacatcaa cagcctggct atattagatg atgagccagt 120
 tatcagaggt ttcatcattg cggaaattgt ggatgctaa gaaatcatgg cctctgaagt 180
 attcacgtct ttccagtacc ctgagttctc tataagatgg cctaacacag gcagaattgg 240
 ccagctactt gtctgcaatt gtatcttcaa gaataccctg gccatccctt tgactgacgt 300
 caagttctct ttggaaagcc tggcatctc ctcactacag acctctgacc atgggacgg 360

gcagcctgg	gagaccatcc	aatcccaa	aaaatgcac	399	
<210>	396				
<211>	403				
<212>	DNA				
<213>	Homo sapiens				
<220>					
<221>	misc_feature				
<222>	(1) ... (403)				
<223>	n = A,T,C or G				
<400>	396				
tggagttntc	agtgc当地 aaca agccataaaag	cttcagttagc	aaattactgt	ctcacagaaa 60	
gacattttca	acttctgctc	cagctgctga	taaaacaaat	catgtgttta	gcttgactcc 120
agacaaggac	aacctgttcc	ttcataactc	tctagagaaa	aaaaggagtt	gttagtagat 180
actaaaaaaa	gtggatgaat	aatctggata	tttttcctaa	aaagattcct	tgaaacacat 240
tagaaaaatg	gagggccta	tgatcagaat	gctagaatta	gtccattgtg	ctgaagcagg 300
gttttagggga	gggagtgagg	gataaaagaa	ggaaaaaaaag	aagagtgaga	aaacctattt 360
atcaaagcag	gtgctatcac	tcaatgttag	gccctgctct	ttt	403
<210>	397				
<211>	100				
<212>	DNA				
<213>	Homo sapiens				
<220>					
<221>	misc_feature				
<222>	(1) ... (100)				
<223>	n = A,T,C or G				
<400>	397				
actagtnncag	tgtggtgaa	ttcgcccccg	cgtcgaccta	naanccatct	ctatagcaaa 60
tccatccccg	ctccctggttg	gtncagaat	gactgacaaa		100
<210>	398				
<211>	278				
<212>	DNA				
<213>	Homo sapiens				
<220>					
<221>	misc_feature				
<222>	(1) ... (278)				
<223>	n = A,T,C or G				
<400>	398				
gcggccgcgt	cgacacagt	tccgccagcg	ctcgccccctg	ggtggggatg	tgctgcacgc 60
ccacactggac	atctggagt	cagccgcctg	gatgaaagag	cggacttcac	ctggggcgat 120
tcactactgt	gcctcgacca	gtgaggagag	ctggaccgac	agcgaggtgg	actcatcatg 180
ctccggccag	cccatccacc	tgtggcagtt	cctcaaggag	ttgctactca	agccccacag 240
ctatggccgc	ttcattangt	ggctcaacaa	ggagaagg		278

ccctttgca ttgccaaatgt ccataaccat gagcactact ctaccatggn tctgc 355

<210> 402

<211> 407

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(407)

<223> n = A,T,C or G

<400> 402

atggggcaag ctggataaaag aaccaagacc cactggagta tgctgtcttc aagaaaaccca 60
 tctcacatgc ggtggcatac ataggctcaa aataaaggaa tggagaaaaa tatttcaagc 120
 aaatggaaaaa cagaaaaaaag caggtgttc actcctactt tctgacaaaaa cagactatgc 180
 gaataaaagat aaaaaagaga aggacattac aaaggtggtc ctgacccttg ataaatctca 240
 ttgcttgata ccaacctggg ctgttttaat tgccaaacc aaaaggataa tttgctgagg 300
 ttgtggagct tctcccctgc agagagtccc tgatctccca aaatttggtt gagatgtaag 360
 gntgattttgc ctgacaactc ctttctgaa gtttactca tttccaa 407

<210> 403

<211> 303

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(303)

<223> n = A,T,C or G

<400> 403

cagtatttat agccnaactg aaaagctagt agcaggcaag tctcaaatcc aggcacccaa 60
 tcctaagcaa gagccatggc atggtaaaaa tgcaaaagga gagtctgcc aatctacaaa 120
 tagagaacaa gacctactca gtcataaca aaaaggcaga caccaacatg gatctcatgg 180
 gggattggat attgttaatta tagagcgaga agatgacagt gatcgtcatt tggcacaaca 240
 tcttaacaac gaccgaaacc cattatttc ataaacctcc attcggtaac catgttgaaa 300
 gga 303

<210> 404

<211> 225

<212> DNA

<213> Homo sapiens

<400> 404

aagtgttaact tttaaaaatt tagtgattt tgaaaattct tagagggaa taaaggaaaa 60
 attgttaatg cactcattt cctttacatg gtgaaagtcc tctttgtatc ctacaaacag 120
 acattttcca ctcgtgttc catagtttt aagtgtatca gatgtgtgg gcatgtgaat 180
 ctccaagtgc ctgtgtataa aataaaagtat ctttatttca ttcatt 225

<210> 405

<211> 334
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(334)
<223> n = A,T,C or G

<400> 405
gagctgttat actgtgagtt ctactaggaa atcatcaaat ctgaggggtt tctggaggac 60
ttcaatacac ctccccccat agtgaatcag cttccagggg gtccagtccc ttccttact 120
tcatccccat cccatgc当地 aggaagaccc tccctcctt gctcacagcc ttctcttaggc 180
ttcccagtgc ctccaggaca gagtggtta tgtttcagc tccatcctt ctgtgagtgt 240
ctggtgcggt tgtgcctcca gtttctgctc agtgcattcat ggacagtgtc cagccatgt 300
cactctccac tctctcanng tggatcccac ccct 334

<210> 406
<211> 216
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(216)
<223> n = A,T,C or G

<400> 406
tttcataacct aatgagggag ttganatnac atnnaaccag gaaatgc当地 gatctcaang 60
gaaacaaaaca cccaaataaac tcggagtggc agactgacaa ctgtgagaca tgcacttgct 120
acnaaacaca aatttnatgt tgcaccctt tttcacacc tgtggttat gacaaagaca 180
actgccaaag aatnttcaag aaggaggact gccant 216

<210> 407
<211> 413
<212> DNA
<213> Homo sapiens

<400> 407
gctgacttgc tagtatcatc tgcattcatt gaagcacaag aacttcatgc cttgactcat 60
gtaaatgc当地 taggattaaa aaataaattt gatatcacat gaaacagac aaaaaatatt 120
gtacaacatt gcacccagtgc ttagattcta cacctggcca ctcaggaagc aagagttaat 180
cccagaggc当地 tatgtcctaa tgtgttatgg caaatggatg tcatgcacgt accttcattt 240
gaaaaattgt catttgtcca tgtgacagtt gataacttatt cacatttcat atggcaacc 300
tgccagacag gagaaagtct tcccatgtt aaagacattt attatctgt tttcctgtca 360
tgggagttcc agaaaaagtt aaaacagaca atggccagg ttctgttagta aag 413

<210> 408
<211> 183
<212> DNA
<213> Homo sapiens

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<220>
<221> misc_feature
<222> (1)...(183)
<223> n = A,T,C or G

<400> 408
ggagctngcc ctcaattcct ccatntctat gttancatat ttaatgtctt ttgnnattaa 60
tncttaacta gttaatcctt aaagggctan ntaatcctta actagtccct ccattgtgag 120
cattatcctt ccagtattcn cttctnttt tatttactcc ttcctggcta cccatgtact 180
ntt 183

<210> 409
<211> 250
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(250)
<223> n = A,T,C or G

<400> 409
cccacgcatt ataagctctt tatttctgta agtcctgcta ggaaatcatc aaatctgacg 60
gtggtttggg ggacctgaac aaacctcctg taattaatca gctttcagtt tctcccccta 120
gtccctcctt caacaacata ggaggatcct ccccttctt ctgctcacgg ctttatctag 180
gttcccagt gcccccagga cagcgtgggc tatgtttaca gcgcntcctt gctggggggg 240
ggccntatgc 250

<210> 410
<211> 306
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(306)
<223> n = A,T,C or G

<400> 410
ggctggtttgc caagaatgaa atgaatgatt ctacagctag gacttaacct taaaatggaa 60
agtcttgc aaaccttgc aggatccgtc tgtgcacatg cctctgtaga gagcagcatt 120
cccagggacc ttggaaacag ttggcactgt aaggtgcttg ctccccaaaga cacatcctaa 180
aaggtgttgt aatgtgaaa accgcttctt cttttattgc cccttcttata ttatgtgaac 240
nactgggtgg cttttttgn atcttttta aactggaaag ttcaatttngaaaatgaata 300
tcntgc 306

<210> 411
<211> 261
<212> DNA
<213> Homo sapiens

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<220>
<221> misc_feature
<222> (1)...(261)
<223> n = A,T,C or G

<400> 411
agagatattn cttaggtnaa agttcataga gttcccatga actatatgac tggccacaca 60
ggatctttt tatttaagga ttctgagatt ttgcttgagc aggatttagat aaggctgttc 120
tttaaatgtc tgaaatggaa cagattcaa aaaaaaaccc cacaatctag ggtgggaaca 180
aggaaggaaa gatgtgaata ggctgatggg caaaaaacca atttaccat cagttccagc 240
cttctctcaa ggngaggcaa a                                         261

<210> 412
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 412
gttcaatgtt acctgacatt tctacaacac cccactcacc gatgtattcg ttgcccaagt 60
gaaacataacc agcctgaatt tggaaaaaat aattgtgttt cttgcccagg aaatactacg 120
actgactttg atggctccac aaacataacc cagtgtaaaa acagaagatg tggaggggag 180
ctgggagatt tcactggta cattgaattc ccaaactacc cangcaatta cccagccaac 240
a                                         241

<210> 413
<211> 231
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(231)
<223> n = A,T,C or G

<400> 413
aactcttaca atccaaagtga ctcatctgtg tgcttgaatc ctttccactg tctcatctcc 60
ctcatccaag tttcttagtac cttcttttg ttgtgaagga taatcaaact gaacaacaaa 120
aagtttactc tcctcatttg gaacctaaaa actctttct tcctgggtct gagggctcca 180
agaatccttg aatcanttct cagatcattg gggacaccan atcaggaacc t             231

<210> 414
<211> 234
<212> DNA
<213> Homo sapiens

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<400> 414
actgtccatg aagcaactgag cagaagctgg aggacacaacg caccagacac tcacagcaag 60
gatggagctg aaaacataac ccactctgtc ctggaggcac tgggaaggct agagaaggct 120
gtgagccaag gagggagggt ttcccttgg catggatgg gatgaagta aggagaggga 180
ctggacccccc tggaagctga ttcactatgg ggggaggtgt attgaagtcc tcca 234

<210> 415
<211> 217
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(217)
<223> n = A,T,C or G

<400> 415
gcataaggatt aagactgagt atctttcta cattttta actttctaag gggcacttct 60
caaaacacag accaggttagc aaatctccac tgctctaagg ntctcaccac cactttctca 120
cacctagcaa tagtagaatt cagtcctact tctgaggcca gaagaatggc tcagaaaaat 180
antggattat aaaaaataac aattaagaaa aataatc 217

<210> 416
<211> 213
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(213)
<223> n = A,T,C or G

<400> 416
atgcatatnt aaagganact gcctcgctt tagaagacat ctggnctgct ctctgcatga 60
ggcacagcag taaagctctt tgattcccaag aatcaagaac tctcccccttc agactattac 120
cgaatgcaag gtggtaatt gaaggccact aattgatgct caaatagaag gatattgact 180
atattggAAC agatggagtc tctactacAA aag 213

<210> 417
<211> 303
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(303)
<223> n = A,T,C or G

<400> 417
nagtcttcag gcccatcagg gaagttcaca ctggagagaa gtcatacata tgtactgtat 60
gtgggaaagg ctttactctg agttcaaatac ttcaagccca tcagagagtc cacactggag 120

agaagccata caaatgcaat gagtgtggga agagcttcag gagggattcc cattatcaag 180
 ttcatctagt ggtccacaca ggagagaaac cctataaatg tgagatatgt gggaaagggt 240
 tcantcaaag ttcttatctt caaatccatc ngttgcata cagtatanan aaacccttta 300
 agt 303

<210> 418
 <211> 328
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1) ... (328)
 <223> n = A,T,C or G

<400> 418
 ttttggcg gggtggggca gggacgggac angagtctca ctctgttgc caggctggag 60
 tgcacaggca tgatctcgcc tcactacaac ccctgcctcc catgtccaag cgattcttg 120
 gcctcagcc tccctgttagc tagaattaca ggcacatgcc accacaccca gctagtttt 180
 gtatTTTtag tagagacagg gtttcaccat gttggccagg ctggctcaa actcctnacc 240
 tcagnggtca ggctggctc aaactcctga cctcaagtga tctgcccacc tcagcctccc 300
 aaagtgtan gattacaggc cgtgagcc 328

<210> 419
 <211> 389
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1) ... (389)
 <223> n = A,T,C or G

<400> 419
 ctcctcaag acggcctgtg gtccgcctcc cggcaaccaa gaagcctgca gtgccatatg 60
 acccctgagc catggactgg agcctgaaag gcagcgtaca ccctgcctcc gatcttgctg 120
 cttgtttctt ctctgtggct ccattcatag cacagttgtt gcaactgaggc ttgtgcaggc 180
 cgagcaaggc caagctggct caaagagcaa ccagtcact ctgcccacggt gtgccaggca 240
 ccggttctcc agccaccaac ctcactcgct cccgcaaatg gcacatcaatg tcttctaccc 300
 taaaggttagg accaaaggc atctgctttt ctgaagtctt ctgctctatc agccatcaacg 360
 tggcagccac tcnggctgtg tcgacgcgg 389

<210> 420
 <211> 408
 <212> DNA
 <213> Homo sapiens

<400> 420
 gttcctccta actcctgcca gaaacagctc tcctcaacat gagagctgca cccctcctcc 60
 tggccaggc agcaagcctt agccttggct tcttggcttgc tcttggcttgc tggtagacc 120
 gaagtgtact agccaaaggag ttgaagttt tgactttgggt gtttcggcat ggagaccgaa 180

gtcccattga caccttccc actgaccca taaaggaatc ctcatggcca caaggatttg 240
 gccaactcac ccagctggc atggagcagc attatgaact tggagagtttataaagaaga 300
 gatataaaaa attcttgaat gagtcctata aacatgaaca ggtttatattt cgaagcacag 360
 acgttgcaccg gactttgatg aagtgcatac acaaaccctgg caagcccg 408

<210> 421

<211> 352

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(352)

<223> n = A,T,C or G

<400> 421

gctcaaaaat cttttactg atnggcattgg ctacacaatc attgactatt acggaggcca 60
 gaggagaatg aggccctggcc tgggagccct gtgcctacta naagcacatt agattatcca 120
 ttcactgaca gaacaggctt ttttgggtc cttttctcc accacnatac acttgcagtc 180
 ctccttctt aagattctt ggcagttgtc tttgtcataa cccacaggtg tagaaaacaag 240
 ggtcaacat gaaatttctg ttcgttagca agtgcatac tcacaaggta gcangtctgc 300
 cactccgagt ttattgggtg tttgttccct ttgagatcca tgcatttccct gg 352

<210> 422

<211> 337

<212> DNA

<213> Homo sapiens

<400> 422

atgccaccaat gctggcaatg cagccccgg tcgaaggccct gcataatccag cccaaagctgg 60
 cgatgatcga cggcaaccgt tgcccaagt tgccgatgcc agccgaagcg gtggtcaagg 120
 gcgatagcaa ggtgccggcg atcgccggcg cgtcaatccct ggccaagggtc agccgtgatc 180
 gtgaaatggc agctgtcgaa ttgatctacc cgggttatgg catcgccggg cataagggtc 240
 atccgacacc ggtgcacctg gaagccttgc agcggctggg gccgacgccc attcaccgac 300
 gttttttcccg ccggtaacggc tggcctatga aaattat 337

<210> 423

<211> 310

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(310)

<223> n = A,T,C or G

<400> 423

gctcaaaaat cttttactg atatggcatg gctacacaat cattgactat tagaggccag 60
 aggagaatga ggcctggcct gggagccctg tgcctactan aagcncatata gattatccat 120
 tcaactgacag aacaggtctt ttgggttcc ttcttctcc ccacgatata cttgcagtc 180
 tccttcttga agattcttgc gcatgttgc ttgtcataac ccacaggtgt anaaacaagg 240

gtgcaacatg aaatttctgt ttcgttagcaa gtgcgtgtct cacagttgtc aagtctgcc 300
 tccgagttta 310

<210> 424
 <211> 370
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(370)
 <223> n = A,T,C or G

<400> 424
 gctcaaaaat cttttactg ataggcatgg ctacacaatc attgactatt agaggccaga 60
 ggagaat gag gcctggcctg ggagccctgt gcctactaga agcacattag attatccatt 120
 cactgacaga acaggtcttt tttgggtctt tcttctccac cacgatatac ttgcagtcc 180
 ccttcttggaa gattcttgg cagttgtctt tgtcataacc cacaggtgta gaaacatcc 240
 ggttgaatct cctgaaactc cctcattagg tatgaaatag catgatgcat tgcataaagt 300
 cacgaaggtg gcaaagatca caacgctgcc cagganaaca ttcattgtga taaggcaggac 360
 tccgtcgacg 370

<210> 425
 <211> 216
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(216)
 <223> n = A,T,C or G

<400> 425
 aattgctatn nttaaaaa ccactcaaaa taattacaa aaaaaaaaaa tnttaaatga 60
 taacaacnca acatcaaggn aaananaaca ggaatggntg actntgcata aatnggccga 120
 anattatcca ttatnttaag ggttgacttc aggntacagc acacagacaa acatgcccag 180
 gaggntntca ggaccgctcg atgtntntg aggagg 216

<210> 426
 <211> 596
 <212> DNA
 <213> Homo sapiens

<400> 426
 cttccagtgaa ggataaccct gttccccgg gccgagggttc tccattaggc tctgattgat 60
 tggcagtcag tgatggaaagg gtgttctgtat cattccgact gcccccaaggg tcgctggcca 120
 gctctctgtt ttgctgagtt ggcagtagga cctaattgt taattaagag tagatggta 180
 gctgtccctg tattttgatt aacctaattgg ccttcccagc acgactcgga ttcagctgga 240
 gacatcacgg caactttaa taaaatgatt tgaagggcca ttaagaggca cttcccgta 300
 ttaggcagg catctgcact gataacttct tggcagctga gctggtcgga gctgtggccc 360
 aaacgcacac ttggctttg gtttgagat acaactctta atcttttagt catgcttgag 420

ggtggatggc ctttcagct ttaacccaat ttgcactgcc ttggaagtgt agccaggaga 480
 atacactcat atactcggtt gcttagaggc cacagcagat gtcattggtc tactgcctga 540
 gtcccgtgg tcccatccca ggaccccca tcggcgagta cctgggagcc cgtgct 596

<210> 427

<211> 107

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(107)

<223> n = A,T,C or G

<400> 427

gaagaattca agttaggttt attcaaaggc cttacngaga atcctanacc caggncagg 60
 cccgggagca gccttanaga gtcctgttt gactgcccgg ctcagng 107

<210> 428

<211> 38

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(38)

<223> n = A,T,C or G

<400> 428

gaacttccna anaangactt tattcactat tttacatt 38

<210> 429

<211> 544

<212> DNA

<213> Homo sapiens

<400> 429

cttgctgga cggaataaaa gtggacgcaa gcatgaccc ctgatgaggg cgctgcattt 60
 attgaagagc ggctgcagcc ctgcgggttca gattaaaatc cgagaattgt atagacgccc 120
 atatccacga actcttgaag gactttctga tttatccaca atcaaatcat cggtttcag 180
 tttggatggt ggctcatcac ctgtagaacc tgacttggcc gtggctgaa tccactcggt 240
 gccttccact tcagttacac ctcactcacc atcctctcct gttggttctg tgctgcttca 300
 agatactaag cccacatttg agatgcagca gccatctccc ccaattcctc ctgtccatcc 360
 ttagtgtcag ttaaaaaatc tgcccttta tgatgtcctt gatgttctca tcaagcccc 420
 gagtttagtt caaagcagta ttcagcgatt tcaagagaag tttttatctt ttgctttgac 480
 acctcaacaa gtttagagaga tatgcataatc cagggatttt ttgccaggtg gtaggagaga 540
 ttat 544

<210> 430

<211> 507

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(507)

<223> n = A,T,C or G

<400> 430

cttatcncaa tggggctccc aaacttggt gtgcagtggaa aactccgggg gaattttgaa 60
 gaacactgac acccatcttc caccggaca ctctgattta attgggctgc agtgagaaca 120
 gagcatcaat ttaaaaagct gcccagaatg ttntcctggg cagcggttgc atcttgccn 180
 cttcggtac tttatgcaat gcatcatgct atttcataacc taatgaggga gttccaggag 240
 attcaaccag gatgtttcta cncctgtggg ttatgacaaa gacaactgcc aaagaatntt 300
 caagaaggag gactgcaagt atatcgttgt ggagaagaag gacccaaaaaa agacctgttc 360
 tgcgtgaa tggataatct aatgtgcttc tagtaggcac agggctccca ggccaggcct 420
 cattctcctc tggcctctaa tagtcaatga ttgtgttagcc atgcctatca gtaaaaagat 480
 tttttagcaaa aaaaaaaaaa aaaaaaaaaa 507

<210> 431

<211> 392

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(392)

<223> n = A,T,C or G

<400> 431

aaaaattcag aatggataaaa aacaaatgaa gtacaaaata tttcagattt acatagcgat 60
 aaacaagaaa gcacttatca ggaggactta caaatggaa tacactctan aaccatcatc 120
 tatcatggct aaatgtgaga ttagcacagc tgttattttt gtacattgca aacacctaga 180
 aagagatggg aaacaaaatc ccaggagttt tgtgtgtgga gtcctgggtt ttccaacaga 240
 catcattcca gcattctgag attagggnga ttgggatca ttctggagtt ggaatgttca 300
 acaaaaagtga tggatgtttagg taaaatgtac aacttctgga tctatgcaga cattgaaggt 360
 gcaatgagtc tggctttac tctgctgttt ct 392

<210> 432

<211> 387

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(387)

<223> n = A,T,C or G

<400> 432

gttatccnta cataatcaaa tatacgatgtt gtacatgttt tcattggngt agattaccac 60
 aatgcaagg caacatgtgt agatctcttgc tcttattttt ttgtctataa tactgttattt 120
 ngtatccaa gctctcggnna gtcggccac tgngaaacat gtccttta gattaacctc 180

gtggacnctn ttgttgnatt gtctgaactg tagngccctg tattttgctt ctgtctgnga 240
 attctgttgc ttctggggca ttccttngt atgcagagga ccaccacaca gatgacagca 300
 atctgaattt ntccaatcac agctgcgatt aagacatact gaaatcgta aggaccggga 360
 acaacgtata gaacactgga gtccttt 387

<210> 433
<211> 281
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(281)
<223> n = A,T,C or G

<400> 433
 ttcaacttagc anagaanact gcttcagggn gtgtaaaatg aaaggcttcc acgcagttat 60
 ctgattaaag aacactaaga gagggacaag gctagaagcc gcaggatgtc tacactatag 120
 caggcnctat ttgggttggc tggaggagct gtggaaaaca tggagagatt ggcgctggag 180
 atcgcgttg ctattcctcn ttgntattac accagngagg ntctctgtnt gcccactgg 240
 tnnaaaacctt ntatacaata atgatagaat aggacacacaca t 281

<210> 434
<211> 484
<212> DNA
<213> Homo sapiens

<400> 434
 ttttaaaata agcatttagt gctcagtccc tactgagttac tctttctctc ccctcctctg 60
 aatttaatcc ttcaacttg caatttgcac ggattacaca tttcactgtt atgtatattt 120
 tggtgcacaaa aaaaaaaaaatgt gtctttgttt aaaattactt ggtttgcac tccatcttgc 180
 ttttccccca ttggaacttag tcattaaccc atctctgaac tggtagaaaa acatctgaag 240
 agcttagtcta tcagcatctg acaggtgaat tggatggttc tcagaaccat ttcacccaga 300
 cagcctgttt ctatcctgtt taataaattt gtttgggttc tctacatgca taacaaaccc 360
 tgctccaatc tgcacataa aagtctgtga cttgaagttt agtcagcacc cccaccaaac 420
 tttatttttc tatgtgtttt ttgcaacata tgagtgtttt gaaaataaaag taccatgtc 480
 ttta 484

<210> 435
<211> 424
<212> DNA
<213> Homo sapiens

<400> 435
 ggcggcgtca gagcagggtca ctttctgcct tccacgtcct ccttcaagga agccccatgt 60
 gggtagctt caatatcgca ggttcttact cctctgcctc tataagctca aaccaccaa 120
 cgatcgggca agtaaaccaccc ctccctcgcc gacttcggaa ctggcgagag ttcagcgcag 180
 atgggcgtgt ggggaggggg caagatagat gagggggagc ggcattgtgc ggggtgaccc 240
 cttggagaga ggaaaaaggc cacaagaggg gctgccaccg ccactaacgg agatggccct 300
 ggttagagacc tttgggggtc tggAACCTC ggactccccca tgctctaact cccacactct 360
 gctatcagaa acttaaactt gaggatttc tctgttttc actcgcaata aattcagagc 420

aaac

424

<210> 436
<211> 667
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(667)
<223> n = A,T,C or G

<400> 436
accttgggaa nactctcaca atataaagggg tcgttagactt tactccaaat tccaaaaagg 60
tcctggccat gtaatcctga aagtttccc aaggtagcta taaaatcctt ataagggtgc 120
agccttcttctt ggaattcctc tgatttcaaa gtctcactct caagttcttg aaaacgaggg 180
cagttcctga aaggcaggta tagcaactga tcttcagaaa gaggaactgt gtgcaccggg 240
atgggctgcc agagtaggat aggattccag atgctgacac cttctggggg aaacagggct 300
gccaggttttgc tcatagact catcaaagtcc cggtcaacgt ctgtgcttcg aatataaacc 360
tgttcatgtt tataggactc attcaagaat tttcttatatc tctttcttat atactctcca 420
agttcataat gctgctccat gcccagctgg gtgagttggc caaatccttg tggccatgag 480
gattccttta tggggtcagt gggaaaggtg tcaatggac ttcggctctcc atggcgaaac 540
accaaagtca caaacttcaa ctccttggtc agtacacttc ggtctagcca gaaaaaaaaagc 600
agaaaacaaga agccaaggct aaggcttgcg gccctgccag gaggaggggt gcagctctca 660
tgtttag 667

<210> 437
<211> 693
<212> DNA
<213> Homo sapiens

<400> 437
ctacgtctca accctcattt ttaggttaagg aatcttaagt ccaaagatata taagtgactc 60
acacagccag gtaagggaaag ctggattggc acactaggac tctaccatac cgggtttgt 120
taaagcttag gtttaggagc tgataagctt ggaaggaact tcagacagct ttttcagatc 180
ataaaaagata attcttagcc catgttcttc tccagagcag acctgaaatg acagcacagc 240
aggtactctt ctatTTTcac ccctcttgct tctactctct ggcagtcaga cctgtggag 300
gccatgggag aaagcagctc tctggatgtt tgtacagatc atggactatt ctctgtggac 360
catttctcca ggttacccta ggtgtcaacta ttggggggac agccagcatc ttttagcttc 420
atTTTgagtt ctgtctgtct tcagtagagg aaactttgc tcttcacact tcacatctga 480
acacctaact gctgttgctc ctgaggttgtt gaaagacaga tatagagctt acagtattta 540
tccttatttctt aggcaactgag ggctgtgggg taccttgc tgccaaaaca gatcctgttt 600
taaggacatg ttgcttcaga gatgtctgtta actatctggg ggctctgttgc gctcttacc 660
ctgcatcatg tgctctcttg gctgaaaatg acc 693

<210> 438
<211> 360
<212> DNA
<213> Homo sapiens

<400> 438

ctgcttatca caatgaatgt tctcctggc agcgttgtga tctttgcac cttcgtaact 60
 ttatgcaatg catcatgcta tttcataacct aatgagggag ttccaggaga ttcaaccagg 120
 atgtttctac acctgtgggt tatgacaag acaactgcc aagaatctc aagaaggagg 180
 actgcaagta tatctgtgg agaagaagga cccaaaaaag acctgttctg tcagtgaatg 240
 gataatctaa tgtgottcta gttaggcacag ggctcccagg ccaggcctca ttctcctctg 300
 gcctctaata gtcaataatt gtgtagccat gcctatcagt aaaaagattt ttgagcaaac 360

<210> 439
 <211> 431
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1) ... (431)
 <223> n = A,T,C or G

<400> 439
 gttcctnnnta actcctgcca gaaacagctc tcctcaacat gagagctgca cccctcctcc 60
 tggccaggc agcaagcctt agccttgct tcttggct gcttttttc tggctagacc 120
 gaagtgtact agccaaggag ttgaagttt tgactttggt gtttcggcat ggagaccgaa 180
 gtcccattga caccttcccc actgacccca taaaggaatc ctcatggcca caaggattt 240
 gccaactcac ccagctggc atggagcagc attatgaact tggagagat ataagaaaga 300
 gatataaaaa attcttgaat gagtcctata aacatgaaca ggtttatatt cgaagcacag 360
 acgttgaccg gactttgatg agtgcatac caaacctggc agcccgatcg cgcggccg 420
 aatttagtag t 431

<210> 440
 <211> 523
 <212> DNA
 <213> Homo sapiens

<400> 440
 agagataaaag cttaggtcaa agttcataga gttccataga actatatgac tggccacaca 60
 gatctttt tatttaagga ttctgagatt ttgcttgagc aggatttagat aaggctgttc 120
 tttaaatgtc tgaaatggaa cagatttcaa aaaaaaacc cacaatctag ggtggaaaca 180
 aggaaggaaa gatgtgaata ggctgtatggg caaaaaaccatttacccat cagttccagc 240
 cttctctcaa ggagaggcaa agaaaggaga tacagtggag acatctgaa agtttctcc 300
 actggaaaac tgctactatc tgttttata tttctgttaa aatatatgag gctacagaac 360
 taaaaattaa aaccttttg tgccttgg tcctgaaaca tttatgttcc ttttaaagaa 420
 aaaaaatca aactttacag aaagatttga tgtatgtaat acatatagca gctcttgaag 480
 tatatatatc atagcaaata agtcatctga tgagaacaag cta 523

<210> 441
 <211> 430
 <212> DNA
 <213> Homo sapiens

<400> 441
 gttcctccta actcctgcca gaaacagctc tcctcaacat gagagctgca cccctcctcc 60
 tggccaggc agcaagcctt agccttgct tcttggct gcttttttc tggctagacc 120

gaagtgtact agccaaggag ttgaagttt tgacttttgt gtttcggcat ggagaccgaa 180
 gtcccattga caccttccc actgacccca taaaggaatc ctcatggcca caaggatttgc 240
 gccaactcac ccagctgggc atggagcagc attatgaact tggagagttataaagaaaga 300
 gatataaaaa attcttgaat gagtcctata aacatgaaca ggtttatatt cgaagcacag 360
 acgttgcaccg gactttgtatg agtgctatga caaacctggc agcccgatcg cgcggccgcg 420
 aatttagtag 430

<210> 442
 <211> 362
 <212> DNA
 <213> Homo sapiens

<400> 442
 ctaaggaatt agtagtgttc ccatcacttg tttggagtgt gctattctaa aagattttga 60
 tttcctggaa tgacaattat atttttaactt tggtggggaa aagagttata ggaccacagt 120
 cttcaacttct gatacttgta attaatctt ttattgcact tgtttgacc attaagctat 180
 atgttttagaa atggtcattt tacggaaaaa ttagaaaaat tctgataataatgcagaata 240
 aatgaattaa tgttttactt aatttatatt gaactgtcaa tgacaataaa aaattctttt 300
 tgattatttt ttgttttcat ttaccagaat aaaaactaag aattaaaagt ttgattacag 360
 tc 362

<210> 443
 <211> 624
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1) ... (624)
 <223> n = A,T,C or G

<400> 443
 tttttttttt gcaacacaat atacatcaca gtgaaatgtg taatccttgc aaattgcaag 60
 ttgaaagaat taaattcaga ggaggggaga gaaagagtac tcagtaggga ctgagcacta 120
 aatgcttatt taaaaagaaa tgtaaagagc agaaagcaat tcaggctacc ctgccttttgc 180
 tgctggctag tactccggtc ggtgtcagca gcacgtggca ttgaacatttgc 240
 cccaaaccac agaaaaatggg gtgaaattgg ccaacttctt attaacttgg cttcctgtttt 300
 tataaaatatt tgtaaataat atcacctact tcaaaggca gttatgaggc ttaaatgaac 360
 taacgcctac aaaacactta aacatagata acatagggtgc aagtactatg tatctggta 420
 atggtaaaca tccttattat taaagtcaac gctaaaatga atgtgtgtgc atatgcta 480
 agtacagaga gagggcactt aaaccaacta agggcctgga gggaaaggttt cctggaaaga 540
 ngatgcttgt gctgggtcca aatcttggtc tactatgacc ttggccaaat tatttaaact 600
 ttgtccctat ctgctaaaca gatc 624

<210> 444
 <211> 425
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature

<222> (1) ... (425)

<223> n = A, T, C or G

<400> 444

gcacatcatt nntcttgcatt ctttgagaa taagaagatc agtaaatagt tcagaagtgg 60
 gaagcttgtt ccaggcctgt gtgtgaaccc aatgtttgc ttagaaatag aacaagtaag 120
 ttcattgcta tagcataaca caaaaattgc ataagtggtg gtcagcaat ccttgaatgc 180
 tgcttaatgt gagaggttgg taaaatcctt tgtcaacac tctaactccc tgaatgttt 240
 gctgtgtgg gacctgtgca tgccagacaa ggccaagctg gctgaaagag caaccagcca 300
 cctctgcaat ctgccaccc ctgctggcag gattgtttt tgcattctgt gaagagccaa 360
 ggaggcacca gggcataagt gatgactt atggcgacg cgccgcgaa tttagtagta 420
 gtaga 425

<210> 445

<211> 414

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1) ... (414)

<223> n = A, T, C or G

<400> 445

catgtttatg nttttggatt actttggca cctagtgttt ctaaatcgctc tatcattctt 60
 ttctgttttt caaaaacgaga gatggccaga gtctcaacaa actgttatctt caagtctttg 120
 tgaaaattctt tgcatgtggc agattattgg atgtatgttc cttaacttag catataaattc 180
 tgggtgtttt cagataaaatg aacagcaaaa tgtggtgaa ttaccatttg gaacattgtg 240
 aataaaaaaat tgtgtctcta gattatgtaa caaataacta ttccctaacc attgatcttt 300
 ggatttttat aatctactc acaaattgact aggcttctcc tcttgttattt tgaagcagtg 360
 tgggtgtggc attgataaaa aaaaaaaaaag tcgacgcggc cgcaattta gtag 414

<210> 446

<211> 631

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1) ... (631)

<223> n = A, T, C or G

<400> 446

acaaaattaga anaaagtggc agagaacacc acataaccttgc tccggaaacat tacaatggct 60
 tctgcatttca tggaaagtgtt gaggatttca tcaatatgcg ggagccatct tgcagggttg 120
 atgctggta tactggacaa cactgtggaa aaaaggacta cagtttctt tacgttggc 180
 ccggctctgt acgatttcag tatgtcttac tcgcagctgt gattggacaa attcagattg 240
 ctgtcatctg tgtggtggtc ctctgcattca caaggccaa acttttagta atagcattgg 300
 actgagattt gtaaaacttcc caaccttcca ggaaatgccc cagaagcaac agaattcaca 360
 gacagaagca aaatacaggg cactacagtt cagacaatac aacaagagcg tccacgaggt 420
 taatctaaag ggagcatgtt tcacagtggc tggactaccg agagcttggc ctacacaata 480

cagtattata gacaaaagaa taagacaaga gatctacaca tggcccttg catttgtgt 540
 aatctacacc aatgaaaaca tgtactacag ctatattga ttatgtatgg atatatttga 600
 aatagtatac attgtcttga tgtttttct g 631

<210> 447
 <211> 585
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(585)
 <223> n = A,T,C or G

<400> 447
 cttggggaaa antntcacaa tataaagggt ctagacttt actccaaatt ccaaaaagg 60
 cctggccatg taatcctgaa agttttcca agtagctat aaaatccta taagggtgca 120
 gcctcttcgt gaattcctct gatttcaaag tctcaactctc aagttcttga aaacgaggc 180
 agttcctgaa aggccaggat agcaactgat cttcagaaag aggaactgtg tgcaccgg 240
 tgggctgccca gagtaggata ggattccaga tgctgacacc ttctggggga aacaggcgt 300
 ccagggttgt catagcactc atcaaagtcc ggtcaacgtc tgcgttcga atataaacct 360
 gttcatgttt ataggactca ttcaagaatt ttctatatct ctttcttata tactctcaa 420
 gttcataatg ctgcctccatg cccagctgg tgagttggcc aaatcctgt ggcattgagg 480
 attcctttat ggggtcagtg ggaaagggtgt caatgggact tcggctccca tgccgaaaca 540
 ccaaagtacaa aacttcaac tccttggcta gtacacttcg gtcta 585

<210> 448
 <211> 93
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(93)
 <223> n = A,T,C or G

<400> 448
 tgctcggtgg tcattctgan nnccgaactg accntgccag ccctgccgan gggcnccat 60
 ggctccctag tgccctggag aggangggc tag 93

<210> 449
 <211> 706
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(706)
 <223> n = A,T,C or G

<400> 449

ccaagttcat gctntgtgct ggacgctgga cagggggcaa aagcnntgc tcgtgggtca 60
 ttctgancac cgaactgacc atgccagccc tgccatgggt cctccatggc tccctagtgc 120
 cctggagagg aggtgtctag tcagagaga gtccttggaa gtggcctctg ngaggagcca 180
 cggggacagc atcctgcaga tggcgcccg cgtccattc gccattcagg ctgcgcaact 240
 gttgggaagg gcgatcggtg cgggcctt cgtattacg ccagctggcg aaagggggat 300
 gtgctgcaag gcgatatagt tggtaacgc cagggtttc ccagtcncga cgttgtaaaa 360
 cgacggccag tgaattgaat ttaggtgaat ctatagaaga gctatgacgt cgcatgcacg 420
 cgtacgttaag cttggatcct etagagcggc cgcctactac tactaaattc gggccgcgt 480
 cgacgtgggat tccnactga gagagtggag agtacatgt gctggacnct gtcctatgaag 540
 cactgagcag aagctggagg cacaacgcncc cagacactca cagctactca ggaggctgag 600
 aacaggttga acctggggagg tggaggttgc aatgagctga gatcaggccn ctgcncccc 660
 gcatggatga cagagtaaa ctccatctta aaaaaaaaaa aaaaaaaaaa 706

<210> 450

<211> 493

<212> DNA

<213> Homo sapiens

<400> 450

gagacggagt gtcactctgt tgcccaggct ggagtgcagc aagacactgt ctaagaaaaa 60
 acagtttaa aaggtaaaac aacataaaaaa gaaatatcct atagtggaaa taagagagtc 120
 aaatgaggt gagaacttta caaaggatc ttacagacat gtcgccaata tcactgcatt 180
 agcctaagta taagaacaac tttggggag aaaccatcat ttgacagtga ggtacaattc 240
 caagtcaggt agtggaaatgg gtggaaattaa actcaaatta atcctgccag ctgaaacgca 300
 agagacactg tcagagagtt aaaaagttagt ttctatccat gaggtgattc cacagtcttc 360
 tcaagtcaac acatctgtga actcacagac caagttctta aaccactgtt caaactctgc 420
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 gcaatttag tag 493

<210> 451

<211> 501

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1) ... (501)

<223> n = A,T,C or G

<400> 451

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 aacgccaggg tttccctgtt cncgacgtt taaaacgacg gccagtgaat tgaatttagg 180
 tgacnctata gaagagctat gacgtcgcat gcacgcgtac gtaagcttgg atcctctaga 240
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 tggagagtga catgtgctgg acnctgtcca tgaagcactg agcagaagct ggaggcaca 360
 cgcnccagac actcacagct actcaggagg ctgagaacag gttgaacctg ggaggtggag 420
 gttgcaatga gctgagatca ggcncnctgcn ccccagcatg gatgacagag taaaactcca 480
 tcttaaaaaa aaaaaaaaaa a 501

<210> 452

<211> 51
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(51)
<223> n = A,T,C or G

<400> 452
agacggtttc accnttacaa cnccttttag gatgggnntt ggggagcaag c 51

<210> 453
<211> 317
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(317)
<223> n = A,T,C or G

<400> 453
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ttcacccana cagcctgttt ctatcctgtt taataaaatta gtttgggttc tctacatgca 180
taacaaaccc tgctccaatc tgtcacataa aagtctgtga cttgaagttt antcagcacc 240
cccaccaaac tttatttttc tatgtgtttt ttgcaacata tgagtgtttt gaaaataagg 300
tacccatgtc tttatta 317

<210> 454
<211> 231
<212> DNA
<213> Homo sapiens

<400> 454
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taagccacgc cacgctcttg aaggagtctt gaattctcct ctgctcactc agtagaaacca 120
agaagaccaa attcttctgc atcccagctt gcaaacaaaa ttgttcttct aggtctccac 180
cttcccttt tcagtgttcc aaagctcctc acaatttcat gaacaacagc t 231

<210> 455
<211> 231
<212> DNA
<213> Homo sapiens

<400> 455
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cattgttccg aatgggcttt ccacaggcta cacacacaaa acaggaaaca tgccaagttt 120
gtttcaacgc attgatgact tctccaagga ttttcctttg gcatcgacca cattcagggg 180
caaagaattt ctcatacgac agctcacaat acagggttcc ttttcctct a 231

<210> 456
<211> 231
<212> DNA
<213> Homo sapiens

<400> 456
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tgcactcaaa ttcccttatac aggaataact acatagccac tatttacaaa gccattggaa 180
ccttttattt tggtcagct gctagtcaact ccctgactga cattgccaag t 231

<210> 457
<211> 231
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(231)
<223> n = A,T,C or G

<400> 457
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tatttgattt tatttagcaat ctcttcaga agacccttga gatcatthaag ctttgtatcc 180
agtgtctaa atcgatgcct catttcctct gaggtgtcgc tggctttgt g 231

<210> 458
<211> 231
<212> DNA
<213> Homo sapiens

<400> 458
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acaccctaaac cttggtaac acgatttggaa attatcattt gggatgagta gaatttccaa 180
ggcctgggt taggcattttt gggggccag accccaggag aagaagattc t 231

<210> 459
<211> 231
<212> DNA
<213> Homo sapiens

<400> 459
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gccctgcact gtttccctc caccacagcc atccctgtccc tcattggctc tgtgctttcc 180
actatacaca gtcaccgtcc caatgagaaa caagaaggag caccctccac a 231

<210> 460

<211> 231
<212> DNA
<213> Homo sapiens

<400> 460
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ccccacccccc cacacgcaca cggccagcct ggagccaca gaagggtcct cctgcagcca 180
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<210> 461
<211> 231
<212> DNA
<213> Homo sapiens

<400> 461
cgagggttga gaagctctaa tgtgcagggg agccgagaag caggcggcct agggagggtc 60
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gtgggggttca gtgaggagtgt gaaaaatttgtt tcagcagaac caagccgttg ggtgaataag 180
agggggatttc catggcactg atagagccct atagttcag agctggaaat t 231

<210> 462
<211> 231
<212> DNA
<213> Homo sapiens

<400> 462
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gaagaactgt tagagagacc aacagggttag tgggttagag atttccagag ttttacattt 180
tctagaggag gtatttaattt ttttctactt catccagtgt tttttttttttt a 231

<210> 463
<211> 231
<212> DNA
<213> Homo sapiens

<400> 463
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catttgcacag gtgtcttttc ctctggacct cggtgtcccc atctgagtga gaaaaggcag 180
tggggaggtg gatcttccag tcgaagcggt atagaagccctt gtgtgaaaag c 231

<210> 464
<211> 231
<212> DNA
<213> Homo sapiens

<400> 464
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aaggacatca catatgaaga atgttaagt tggaggtggc aacgtgaattt gcaaacaggg 120

cctgcttcag tgactgtgt cctgttagtcc cagctactcg ggagtctgtg tgaggccagg 180
 ggtgccagcg caccagctag atgctctgta actttctaggc cccatttcc c 231

<210> 465

<211> 231

<212> DNA

<213> Homo sapiens

<400> 465

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 aggatggcac aatttttgc tttgttccata atataactcag attagttcag ctccatcaga 180
 taaaactggag acatgcagga cattaggta gtgtttagc tctggtaatg a 231

<210> 466

<211> 231

<212> DNA

<213> Homo sapiens

<400> 466

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 cctgtgcaat caaatattgt ggagaattcc ctagtggag aagtccacaaa gactataggc 180
 aataatggag accagtcccc caagatgaca accagtcgtt gtgtgcggct g 231

<210> 467

<211> 311

<212> DNA

<213> Homo sapiens

<400> 467

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 gcatgggtct ctgccaagc tcgtaatgag actatacgaa ggcggctgtg ggacgtcagt 240
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<210> 468

<211> 3112

<212> DNA

<213> Homo sapiens

<400> 468

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 tttgtccttgc tagttaattt gaaagaaatag ggcacttgc tgagccactt taggttccac 3060
 tcctggcaat aaagaatttcaaaagagcaa aaaaaaaaaa aaaaaaaaaa aa 3112

<210> 469

<211> 2229

<212> DNA

<213> Homo sapiens

<400> 469

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<210> 470

<211> 2426

<212> DNA

<213> Homo sapiens

<400> 470

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gcatgaattc tgtgaaaago ttgttgata ttgtgataga gatagagaaa tgaagtatat 240  
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<210> 471  
<211> 812  
<212> DNA  
<213> Homo sapiens
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<210> 472
<211> 515
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(515)
<223> n = A,T,C or G

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<210> 473
<211> 5829
<212> DNA
<213> Homo sapiens

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<211> 1594

<212> DNA

<213> Homo sapiens

<400> 474

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<212> DNA

<213> Homo sapiens

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<400> 475

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<212> DNA

<213> Homo sapiens

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<211> 141
<212> PRT
<213> Homo sapiens

<400> 477
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Leu Ser His Tyr His Arg Asp Thr Arg His His Thr Val Thr Trp Thr
35 40 45

His His His Thr His Glu His Thr Asp Thr Leu Pro Tyr Gly His Trp
50 55 60

His Thr His Cys His Thr Val Thr Trp Thr His Leu His Thr Ile Thr
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Pro Pro His Thr Leu Pro Val Asp Thr Arg Thr His Arg His Cys His
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Thr Asp Thr Gln Asn Thr Val Thr Arg Arg His His His Ala Asp Thr
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Pro Pro Leu Trp Cys Arg Leu Asn Tyr Pro Ala Gly Gly Thr Ala Val
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Ala Tyr Ser Cys Leu Ser Asp Trp Leu Ser Pro Gln
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<210> 478

<211> 144

<212> PRT

<213> Homo sapiens

<400> 478

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Gly Glu Ile Thr Trp Thr His His His Thr Ile Thr Gly Thr Gln Thr
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His Gly Asp Ile Thr Thr Trp Thr His Cys His Thr Thr Thr Gly Thr
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Arg Asp Ile Thr Leu Ser His Gly His Thr Ile Thr His Met Asn Thr
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Pro Thr His Cys His Met Asp Thr Gly Thr His Thr Ala Thr Leu Ser
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His Gly His Thr Ser Thr Pro Ser His His His Thr His Cys Leu Trp
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Thr Gln Gly His Thr Asp Thr Val Thr Gln Ile His Lys Thr Leu Ser
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His Gly Asp Ile Thr Met Gln Ile His His His Ser Gly Ala Val
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<210> 479

<211> 223

<212> PRT

<213> Homo sapiens

<400> 479

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35 40 45															
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Arg Asp Ile Thr Leu Ser His Gly His Thr Ile Thr His Met Asn Thr															
65 70 75 80															
Pro Thr His Cys His Met Asp Thr Ala Thr His Thr Ala Thr Leu Ser															
85 90 95															
His Gly His Thr Ser Ile Pro Ser His His His Thr His Cys His Val															
100 105 110															
Asp Thr Arg Thr His Arg His Cys His Thr Asp Thr Gln Asn Thr Val															
115 120 125															
Thr Arg Arg His His His Ala Asp Thr Pro Pro His Gly His Ser Thr															
130 135 140															
Arg His Ser Ala Thr Gln Ile His His His Thr Glu Met Arg Thr His															
145 150 155 160															
Cys His Thr Asp Thr Thr Ser Leu Pro His Phe His Val Ser Ala															
165 170 175															
Gly Gly Val Gly Pro Thr Thr Leu Gly Ser Asn Arg Glu Ile Thr Trp															
180 185 190															
Thr Tyr Ser Glu Gly Lys Ile Phe Phe Tyr Phe Leu Gly Asn Gln Ala															
195 200 205															
Arg Leu Cys Leu Lys Lys Arg Lys Lys Lys Gln Tyr Thr Val															
210 215 220															

<210> 480

<211> 145

<212> PRT

<213> Homo sapiens

<400> 480

<210> 481
<211> 168
<212> PRT
<213> *Homo sapiens*

Cys Pro Ala Ala Ser Glu Val Gly Gly Cys Ala Pro Ser Ser Trp Arg
85 90 95

Ala Leu Ala Glu Val Thr Gly Cys Ser Leu Gly Pro Leu Gly Leu Ala
100 105 110

Gln His Ala Gln Ala Ser Val Leu Leu Leu Cys Tyr Lys Trp Ser His
115 120 125

Ile Gly Glu Thr Ser Ser His Leu Arg Ser Lys Val Tyr Ala Ala Phe
 130 135 140

Gly Gly Ser Ser Pro Cys Leu Lys Gly Leu Met Ser Leu Trp Ala Ser
 145 150 155 160

Trp Leu Ser Arg Gly Arg Pro
165

<210> 482

<211> 144

<212> PRT

<213> Homo sapiens

<400> 482

Met Glu Pro Tyr Arg Gly Asn Lys Lys Gln Val Gln Glu Lys Gly Val
5 10 15

Pro Cys Leu Trp Gly Ser Ser Pro Cys Leu Arg Cys His Met Ala Leu
20 25 30

Arg Ala Ser Trp Leu Pro Gly Gly Gly Pro Gln Ala Ile Leu Gly Arg
35 40 45

Thr Leu Cys Ser Ser Ala Glu Ser Ser Gln Asp Cys His Pro Gly GLY
50 55 60

Pro Ser Ile Ala Leu Ala Lys Pro Cys Arg Gly Val Trp Leu Leu Phe
65 70 75 80

Glu Pro Ala Trp Pro Pro Trp His Ala Arg Ala Pro Gly Ala Gly Thr
85 90 95

Leu Leu Arg Val Cys Leu Ser Cys Leu Gly Cys His Leu Cys Gly Gly
100 105 110

Ala Ser Gly Gly Gly Pro Ala Thr Asn Leu Thr Gln Ser Arg Lys
115 120 125

Trp Met Ala Met Phe Pro Gln Pro Glu Trp Leu Pro Pro Asp Gly

130

135

140

<210> 483
<211> 144
<212> PRT
<213> Homo sapiens

<400> 483
Met Glu Thr Gln Arg Gly Asn Lys Gln Arg Ala Gln Glu Gln Gly Val
5 10 15
Cys Cys Leu Trp Gly Ser Ser Pro Cys Leu Gly Ser Tyr Gly Thr Ala
20 25 30
Gly Phe Leu Val Ala Lys Arg Arg Thr Thr Gly Leu Leu Glu Glu Asp
35 40 45
Phe Thr Phe Lys Cys Arg Lys Gln Pro Lys Leu Pro Ser Met Arg Leu
50 55 60
Ser Leu Leu Trp Pro Trp Arg Asp Leu Lys Phe Val Pro Arg Gln Asp
65 70 75 80
Lys Leu Thr Arg Ser Ser Val Ser Val Ala Gly Ala Tyr Ala Cys Arg
85 90 95
Ala Gly Pro Gly Trp Leu Lys Glu Gln Pro Ala Thr Ser Ala Arg Val
100 105 110
Arg Leu Val Gln Ala Glu His Pro Pro Pro His Pro Leu Glu Glu Val
115 120 125
Gly Met Ala Arg Phe Pro Gln Pro Glu Cys Leu Pro Pro Tyr Cys
130 135 140

<210> 484
<211> 30
<212> PRT
<213> Homo Sapien

<400> 484
Thr Ala Ala Ser Asp Asn Phe Gln Leu Ser Gln Gly Gly Gln Gly Phe
1 5 10 15
Ala Ile Pro Ile Gly Gln Ala Met Ala Ile Ala Gly Gln Ile
20 25 30

<210> 485
<211> 31
<212> DNA
<213> Artificial Sequence

<220>			
<223> Made in a lab			
<400> 485			
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<211> 36			
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<210> 488			
<211> 33			
<212> DNA			
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<220>			
<223> Made in a lab			
<400> 488			
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<210> 489			
<211> 19			
<212> PRT			
<213> Artificial Sequence			
<220>			
<223> Made in a lab			
<400> 489			
Met Asp Arg Leu Val Gln Arg Phe Gly Thr Arg Ala Val Tyr Leu Ala			
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Ser Val Ala

<210> 490
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 490
Tyr Leu Ala Ser Val Ala Ala Phe Pro Val Ala Ala Gly Ala Thr Cys
1 5 10 15
Leu Ser His Ser
20

<210> 491
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 491
Thr Cys Leu Ser His Ser Val Ala Val Val Thr Ala Ser Ala Ala Leu
1 5 10 15
Thr Gly Phe Thr
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<210> 492
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 492
Ala Leu Thr Gly Phe Thr Phe Ser Ala Leu Gln Ile Leu Pro Tyr Thr
1 5 10 15
Leu Ala Ser Leu
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<210> 493
<211> 20
<212> PRT
<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 493

Tyr Thr Leu Ala Ser Leu Tyr His Arg Glu Lys Gln Val Phe Leu Pro
1 5 10 15
Lys Tyr Arg Gly
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<210> 494

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 494

Leu Pro Lys Tyr Arg Gly Asp Thr Gly Gly Ala Ser Ser Glu Asp Ser
1 5 10 15
Leu Met Ile Ser
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<210> 495

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 495

Asp Ser Leu Met Thr Ser Phe Leu Pro Gly Pro Lys Pro Gly Ala Pro
1 5 10 15
Phe Pro Asn Gly
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<210> 496

<211> 21

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 496

Ala Pro Phe Pro Asn Gly His Val Gly Ala Gly Gly Ser Gly Leu Leu
1 5 10 15
Pro Pro Pro Pro Ala
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<210> 497
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 497
Leu Leu Pro Pro Pro Ala Leu Cys Gly Ala Ser Ala Cys Asp Val
1 5 10 15
Ser Val Arg Val
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<210> 498
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 498
Asp Val Ser Val Arg Val Val Val Gly Glu Pro Thr Glu Ala Arg Val
1 5 10 15
Val Pro Gly Arg
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<210> 499
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 499
Arg Val Val Pro Gly Arg Gly Ile Cys Leu Asp Leu Ala Ile Leu Asp
1 5 10 15
Ser Ala Phe Leu
20

<210> 500
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 500

Leu Asp Ser Ala Phe Leu Leu Ser Gln Val Ala Pro Ser Leu Phe Met
 1 5 10 15

Gly Ser Ile Val
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<210> 501
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 501
Phe Met Gly Ser Ile Val Gln Leu Ser Gln Ser Val Thr Ala Tyr Met
 1 5 10 15
Val Ser Ala Ala
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<210> 502
<211> 414
<212> DNA
<213> Homo Sapien

<400> 502
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ctgttagagtt ttttggaaatng acctcagtag caatgcaatg agctgggtcc gccaggctcc 180
agggaaagggg ctggaaatgga tcggagccat tgataattgt ccacantacg cgacactgggc 240
gaaaggccga tttnatnattt ccaaaaacctn gaccacggtg gatttggaaaa tgaccagtcc 300
gacaaccgag gacacggcca cctatTTTg tggcagaatg aatactggta atagtggttg 360
gaagaatatt tggggcccaag' gcaccctggc caccgtntcc tcagggcaac ctaa 414

<210> 503
<211> 379
<212> DNA
<213> Homo Sapien

<400> 503
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ctggtcacgc ctgggacacc cctgacactc acctgcacccg tntctggatt ngacatcagt 120
agctatggag tgagctgggt ccgccaggt ccagggaagg ggctggnata catcgatca 180
tttagtagtag tggtagatatt tacgcgagct gggcgaaagg ccgattcacc atttccaaaa 240
cctngaccac ggtggatttg aaaatcacca gtttgacaac cgaggacacg gccacctatt 300
tntgtgccag aggggggttt aattataaag acatttgggg cccaggcacc ctggtcacccg 360
tntccttagg gcaacctaa 379

<210> 504
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 504
Gly Phe Thr Asn Tyr Thr Asp Phe Glu Asp Ser Pro Tyr Phe Lys Glu
1 5 10 15
Asn Ser Ala

<210> 505
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 505
Lys Glu Asn Ser Ala Phe Pro Pro Phe Cys Cys Asn Asp Asn Val Thr
1 5 10 15
Asn Thr Ala Asn
20

<210> 506
<211> 407
<212> DNA
<213> Homo Sapien

<400> 506
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accgtctctg gattctccct cagtagcaat gcaatgatct gggtccgcca ggctccaggg 180
aaggggctgg aatacatcg atacattagt tatggtggtg ggcatacta cgcgagctgg 240
gtgaaaggcc gattcaccat ctccaaaacc tcgaccacgg tggatctgag aatgaccagt 300
ctgacaacctt aggacacggc cacctatttc tggccagaa atagtgattt tagtggatg 360
ttgtggggcc caggcaccct ggtcaccgtc tcctcaggc aacctaa 407

<210> 507
<211> 422
<212> DNA
<213> Homo Sapien

<400> 507
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tcgggtggagg agtccgggg tcgcctggc acgcctggg caccctgac actcacctgt 120
acagtctctg gattctccct cagcaactac gacactgaact gggtccgcca ggctccaggg 180
aaggggctgg aatggatcg gatcattaat tatggtggtg ggacggacta cgcgactgg 240
gcaaaaggcc ggttcaccat ctccaaaacc tcgaccacgg tggatctcaa gatgccagt 300
ccgacaacctt aggacacggc cacctatttc tggccagag ggtggaaagtg cgatgagtct 360

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aa 422

<210> 508
<211> 411
<212> DNA
<213> Homo Sapien

<400> 508 60
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cggtgagga gtccgggggt cgccctggta cgccctggac acccctgaca ctcacctgca 180
cagtctctgg aatcgacccctc agtagctact gcatgagctg ggtccggccag gctccaggga 240
aggggctgga atggatcggta atcattggta ctccctggta cacatactac gcgaggtggg 300
cgaaaaggccg attcaccatc tccaaaacct cgaccacggc gcatntgaaa atcnccagtc 360
cgacaaccga ggacacggcc acctatttct gtgccagaga tcttcggat ggtagtagta
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<210> 509
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 509
Leu Cys Lys Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Ala Ser
1 5 10 15

<210> 510
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 510
Pro Glu Tyr Asn Arg Pro Leu Leu Ala Asn Asp Leu Met Leu Ile
1 5 10 15

<210> 511
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 511

Tyr His Pro Ser Met Phe Cys Ala Gly Gly Gln Asp Gln Lys
1 5 10 15

<210> 512
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 512
Asp Ser Gly Gly Pro Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu
1 5 10 15

<210> 513
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 513
Ala Pro Cys Gly Gln Val Gly Val Pro Asx Val Tyr Thr Asn Leu
1 5 10 15

<210> 514
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 514
Leu Cys Lys Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Ala Ser
1 5 10 15

<210> 515
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 515
Met Val Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg
1 5 10 15

<210> 516
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 516

Val	Ser	Glu	Ser	Asp	Thr	Ile	Arg	Ser	Ile	Ser	Ile	Ala	Ser	Gln
1				5					10					15

<210> 517
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 517

Glu	Val	Cys	Ser	Lys	Leu	Tyr	Asp	Pro	Leu	Tyr	His	Pro	Ser	Met
1					5				10					15

<210> 518
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 518

Arg	Ala	Glu	Pro	Gly	Thr	Glu	Ala	Arg	Arg	His	Tyr	Asp	Glu	Gly
1					5				10					15

<210> 519
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 519

Arg	Ala	Glu	Pro	Gly	Thr	Glu	Ala	Arg	Arg	Asn	Tyr	Asp	Glu	Gly	Cys
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Gly															

<210> 520

<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 520
Val Gly Glu Gly Leu Tyr Gln Gly Val Pro Arg Ala Glu Pro Gly Thr
1 5 10 15
Glu Ala Arg Arg His Tyr Asp Glu Gly
20 25

<210> 521
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 521
Ala Pro Phe Pro Asn Gly His Val Gly Ala Gly Ser Gly Leu Leu
1 5 10 15
Pro Pro Pro Pro Ala
20

<210> 522
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 522
Leu Leu Val Val Pro Ala Ile Lys Lys Asp Tyr Gly Ser Gln Glu Asp
1 5 10 15
Phe Thr Gln Val
20

<210> 523
<211> 254
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 523
Met Ala Thr Ala Gly Asn Pro Trp Gly Trp Phe Leu Gly Tyr Leu Ile

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20		25												30	
Asn	Gly	Glu	Asp	Cys	Ser	Pro	His	Ser	Gln	Pro	Trp	Gln	Ala	Ala	Leu
35								40					45		
Val	Met	Glu	Asn	Glu	Leu	Phe	Cys	Ser	Gly	Val	Leu	Val	His	Pro	Gln
50								55				60			
Trp	Val	Leu	Ser	Ala	Thr	His	Cys	Phe	Gln	Asn	Ser	Tyr	Thr	Ile	Gly
65					70					75				80	
Leu	Gly	Leu	His	Ser	Leu	Glu	Ala	Asp	Gln	Glu	Pro	Gly	Ser	Gln	Met
85									90				95		
Val	Glu	Ala	Ser	Leu	Ser	Val	Arg	His	Pro	Glu	Tyr	Asn	Arg	Pro	Leu
									105				110		
100															
Leu	Ala	Asn	Asp	Leu	Met	Leu	Ile	Lys	Leu	Asp	Glu	Ser	Val	Ser	Glu
								115		120			125		
Ser	Asp	Thr	Ile	Arg	Ser	Ile	Ser	Ile	Ala	Ser	Gln	Cys	Pro	Thr	Ala
									130		135		140		
Gly	Asn	Ser	Cys	Leu	Val	Ser	Gly	Trp	Gly	Leu	Leu	Ala	Asn	Gly	Arg
								145		150		155		160	
Met	Pro	Thr	Val	Leu	Gln	Cys	Val	Asn	Val	Ser	Val	Val	Ser	Glu	Glu
									165		170		175		
Val	Cys	Ser	Lys	Leu	Tyr	Asp	Pro	Leu	Tyr	His	Pro	Ser	Met	Phe	Cys
								180		185		190			
Ala	Gly	Gly	Gly	Gln	Xaa	Gln	Xaa	Asp	Ser	Cys	Asn	Gly	Asp	Ser	Gly
								195		200		205			
Gly	Pro	Leu	Ile	Cys	Asn	Gly	Tyr	Leu	Gln	Gly	Leu	Val	Ser	Phe	Gly
								210		215		220			
Lys	Ala	Pro	Cys	Gly	Gln	Val	Gly	Val	Pro	Gly	Val	Tyr	Thr	Asn	Leu
								225		230		235		240	
Cys	Lys	Phe	Thr	Glu	Trp	Ile	Glu	Lys	Thr	Val	Gln	Ala	Ser		
								245				250			

<210> 524

<211> 765

<212> DNA

<213> Homo sapien

<400> 524

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aagttggacg	aatccgtgtc	cgagtctgac	accatccgga	gcatcagcat	tgcttcgcag	420
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atgccttaccg	tgctgcagtg	cgtgaacgtg	tcgggtgggt	ctgaggaggt	ctgcagtaag	540
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gactccctgca	acgggtgactc	tggggggccc	ctgatctgca	acgggtactt	gcagggcctt	660
gtgtctttcg	aaaaagcccc	gtgtggccaa	gttggcgtgc	caggtgtcta	caccaacctc	720
tgcaaattca	ctgagtggat	agagaaaaacc	gtccaggcca	gttaa		765

<210> 525
<211> 254
<212> PRT
<213> Homo sapien

<400> 525

Met	Ala	Thr	Ala	Gly	Asn	Pro	Trp	Gly	Trp	Phe	Leu	Gly	Tyr	Leu	Ile
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	20							25						30	
Asn	Gly	Glu	Asp	Cys	Ser	Pro	His	Ser	Gln	Pro	Trp	Gln	Ala	Ala	Leu
	35							40					45		
Val	Met	Glu	Asn	Glu	Leu	Phe	Cys	Ser	Gly	Val	Leu	Val	His	Pro	Gln
	50						55				60				
Trp	Val	Leu	Ser	Ala	Ala	His	Cys	Phe	Gln	Asn	Ser	Tyr	Thr	Ile	Gly
	65						70				75		80		
Leu	Gly	Leu	His	Ser	Leu	Glu	Ala	Asp	Gln	Glu	Pro	Gly	Ser	Gln	Met
	85						90					95			
Val	Glu	Ala	Ser	Leu	Ser	Val	Arg	His	Pro	Glu	Tyr	Asn	Arg	Pro	Leu
	100						105					110			
Leu	Ala	Asn	Asp	Leu	Met	Leu	Ile	Lys	Leu	Asp	Glu	Ser	Val	Ser	Glu
	115						120					125			
Ser	Asp	Thr	Ile	Arg	Ser	Ile	Ser	Ile	Ala	Ser	Gln	Cys	Pro	Thr	Ala
	130						135				140				
Gly	Asn	Ser	Cys	Leu	Val	Ser	Gly	Trp	Gly	Leu	Leu	Ala	Asn	Gly	Arg
	145						150				155		160		
Met	Pro	Thr	Val	Leu	Gln	Cys	Val	Asn	Val	Ser	Val	Val	Ser	Glu	Glu
	165						170					175			
Val	Cys	Ser	Lys	Leu	Tyr	Asp	Pro	Leu	Tyr	His	Pro	Ser	Met	Phe	Cys
	180						185				190				
Ala	Gly	Gly	Gln	Asp	Gln	Lys	Asp	Ser	Cys	Asn	Gly	Asp	Ser	Gly	
	195					200				205					
Gly	Pro	Leu	Ile	Cys	Asn	Gly	Tyr	Leu	Gln	Gly	Leu	Val	Ser	Phe	Gly
	210						215				220				
Lys	Ala	Pro	Cys	Gly	Gln	Val	Gly	Val	Pro	Gly	Val	Tyr	Thr	Asn	Leu
	225					230				235			240		
Cys	Lys	Phe	Thr	Glu	Trp	Ile	Glu	Lys	Thr	Val	Gln	Ala	Ser		
						245					250				

<210> 526
<211> 963
<212> DNA
<213> Homo sapiens

<400> 526

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aactgcacatcg tggtcttcat cgtaaggacg gaacgcagcc tgcacgctcc gatgtacctc 180
tttctctgca tgcttgcagc cattgacctg gccttatcca catccaccat gcctaagatc 240
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 gcccagattt gcategtggc tgtggccgc ggatccctt ttttttccc actgcctcg 480
 ctgatcaagc ggctggcctt ctgccactcc aatgtcctt cgcactccta ttgtgtccac 540
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 tga 963

<210> 527
<211> 321
<212> PRT
<213> Homo sapiens

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Met Tyr Val Val Ala Met Phe Gly Asn Cys Ile Val Val Phe Ile Val
35 40 45

Arg Thr Glu Arg Ser Leu His Ala Pro Met Tyr Leu Phe Leu Cys Met
50 55 60

Leu Ala Ala Ile Asp Leu Ala Leu Ser Thr Ser Thr Met Pro Lys Ile
65 70 75 80

Leu Ala Leu Phe Trp Phe Asp Ser Arg Glu Ile Ser Phe Glu Ala Cys
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Leu Thr Gln Met Phe Phe Ile His Ala Leu Ser Ala Ile Glu Ser Thr
100 105 110

Ile Leu Leu Ala Met Ala Phe Asp Arg Tyr Val Ala Ile Cys His Pro
115 120 125

Leu Arg His Ala Ala Val Leu Asn Asn Thr Val Thr Ala Gln Ile Gly
130 135 140

Ile Val Ala Val Val Arg Gly Ser Leu Phe Phe Phe Pro Leu Pro Leu
145 150 155 160

Leu Ile Lys Arg Leu Ala Phe Cys His Ser Asn Val Leu Ser His Ser
165 170 175

Tyr Cys Val His Gln Asp Val Met Lys Leu Ala Tyr Ala Asp Thr Leu
 180 185 190

Pro Asn Val Val Tyr Gly Leu Thr Ala Ile Leu Leu Val Met Gly Val
 195 200 205

Asp Val Met Phe Ile Ser Leu Ser Tyr Phe Leu Ile Ile Arg Thr Val
 210 215 220

Leu Gln Leu Pro Ser Lys Ser Glu Arg Ala Lys Ala Phe Gly Thr Cys
 225 230 235 240

Val Ser His Ile Gly Val Val Leu Ala Phe Tyr Val Pro Leu Ile Gly
 245 250 255

Leu Ser Val Val His Arg Phe Gly Asn Ser Leu His Pro Ile Val Arg
 260 265 270

Val Val Met Gly Asp Ile Tyr Leu Leu Leu Pro Pro Val Ile Asn Pro
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Met Phe Lys Ile Ser Cys Asp Lys Asp Leu Gln Ala Val Gly Gly Lys
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<212> DNA

<213> Homo Sapien

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<210> 529

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<212> DNA

<213> Homo Sapien

<400> 529

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20

<210> 530

<211> 1852

<212> DNA

<213> Homo sapiens

<400> 530

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 <213> Homo sapiens

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<211> 293
<212> PRT
<213> Homo sapiens

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20 25 30

Val Lys Thr Leu Gly Ser Lys Arg Cys Lys Trp Cys Cys His Cys Phe
35 40 45

Pro Cys Cys Arg Gly Ser Gly Lys Ser Asn Val Val Ala Trp Gly Asp
50 55 60

Tyr Asp Asp Ser Ala Phe Met Asp Pro Arg Tyr His Val His Gly Glu
65 70 75 80

Asp Leu Asp Lys Leu His Arg Ala Ala Trp Trp Gly Lys Val Pro Arg
85 90 95

Lys Asp Leu Ile Val Met Leu Arg Asp Thr Asp Val Asn Lys Arg Asp
100 105 110

Lys Gln Lys Arg Thr Ala Leu His Leu Ala Ser Ala Asn Gly Asn Ser
115 120 125

Glu Val Val Lys Leu Val Leu Asp Arg Arg Cys Gln Leu Asn Val Leu
130 135 140

Asp Asn Lys Lys Arg Thr Ala Leu Thr Lys Ala Val Gln Cys Gln Glu
145 150 155 160

Asp Glu Cys Ala Leu Met Leu Leu Glu His Gly Thr Asp Pro Asn Ile
165 170 175

Pro Asp Glu Tyr Gly Asn Thr Thr Leu His Tyr Ala Val Tyr Asn Glu
180 185 190

Asp Lys Leu Met Ala Lys Ala Leu Leu Leu Tyr Gly Ala Asp Ile Glu
195 200 205

Ser Lys Asn Lys His Gly Leu Thr Pro Leu Leu Leu Gly Ile His Glu
210 215 220

Gln Lys Gln Gln Val Val Lys Phe Leu Ile Lys Lys Lys Ala Asn Leu

225	230	235	240
Asn Ala Leu Asp Arg Tyr Gly Arg Thr Ala Leu Ile Leu Ala Val Cys			
245		250	255
Cys Gly Ser Ala Ser Ile Val Ser Pro Leu Leu Glu Gln Asn Val Asp			
260		265	270
Val Ser Ser Gln Asp Leu Glu Arg Arg Pro Glu Ser Met Leu Phe Leu			
275	280	285	
Val Ile Ile Met			
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<212> DNA
<213> Homo sapiens

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<210> 534
<211> 267
<212> PRT
<213> Homo sapiens

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Arg Lys Gln Ala Ala Gly Ser Gly Ala Gly Tyr Ala Leu Pro Ser Ala
20 25 30
Leu Gln Ser Met Pro Gln Gly Ser Tyr Ala Thr Ala Arg Phe Leu Val
35 40 45

Ala Lys Arg Pro Thr Thr Gly His Leu Glu Lys Glu Phe Met Phe His
 50 55 60

Cys Arg Lys Gln Pro Gly Ser Pro Ser Arg Gly Leu Gly Leu Leu Trp
 65 70 75 80

Pro Trp Pro Asp Ile Glu Phe Val Pro Arg Gln Asp Lys Leu Thr Gln
 85 90 95

Ser Ser Val Leu Val Pro Gln Ile Cys Ala Cys Gln Thr Arg Pro Asn
 100 105 110

Trp Leu Asn Glu Gln Pro Ala Thr Ser Ala Gly Val Arg Leu Glu Glu
 115 120 125

Val Asp Gln Pro Pro Thr Leu Pro Ser Gln Gly Ser Gly Trp Pro Cys
 130 135 140

Ser His Ser Leu Ser Gly Cys His Leu Met Ala Asp Ile Ala Lys Ala
 145 150 155 160

Leu Gly Lys Ala Asp Gly Pro Trp Pro Tyr Leu Phe Val Arg Arg Thr
 165 170 175

Asp Val Pro Cys Pro Ala Ala Ser Glu Val Gly Gly Cys Ala Pro Ser
 180 185 190

Ser Trp His Thr Leu Ala Glu Val Thr Gly Cys Ser Leu Ser Pro Leu
 195 200 205

Ser Leu Ala Gln His Ala Gln Ala Ser Val Leu Leu Leu Cys Tyr Lys
 210 215 220

Trp Ser His Ile Gly Glu Thr Ser Ser His Leu Arg Ser Lys Val Tyr
 225 230 235 240

Ala Ala Phe Gly Gly Ser Ser Pro Cys Leu Lys Gly Leu Met Ser Leu
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Trp Ala Ser Trp Leu Pro Arg Gly Arg Pro
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<211> 6082

<212> DNA

<213> Homo sapiens

<400> 535

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<213> Homo sapiens

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<222> (4535)
<223> n=A,T,C or G

<400> 536

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<400> 537
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 Ile Gly His Lys Arg Arg Leu Glu Glu Asp Asp Met Tyr Ser Val Leu
 35 40 45
 Pro Glu Asp Arg Ser Gln His Leu Gly Glu Glu Leu Gln Gly Phe Trp
 50 55 60
 Asp Lys Glu Val Leu Arg Ala Glu Asn Asp Ala Gln Lys Pro Ser Leu
 65 70 80
 Thr Arg Ala Ile Ile Lys Cys Tyr Trp Lys Ser Tyr Leu Val Leu Gly
 85 90 95
 Ile Phe Thr Leu Ile Glu Glu Ser Ala Lys Val Ile Gln Pro Ile Phe
 100 105 110
 Leu Gly Lys Ile Ile Asn Tyr Phe Glu Asn Tyr Asp Pro Met Asp Ser
 115 120 125
 Val Ala Leu Asn Thr Ala Tyr Ala Tyr Ala Thr Val Leu Thr Phe Cys
 130 135 140
 Thr Leu Ile Leu Ala Ile Leu His His Leu Tyr Phe Tyr His Val Gln
 145 150 155 160
 Cys Ala Gly Met Arg Leu Arg Val Ala Met Cys His Met Ile Tyr Arg
 165 170 175

Lys Ala Leu Arg Leu Ser Asn Met Ala Met Gly Lys Thr Thr Thr Gly
 180 185 190

 Gln Ile Val Asn Leu Leu Ser Asn Asp Val Asn Lys Phe Asp Gln Val
 195 200 205

 Thr Val Phe Leu His Phe Leu Trp Ala Gly Pro Leu Gln Ala Ile Ala
 210 215 220

 Val Thr Ala Leu Leu Trp Met Glu Ile Gly Ile Ser Cys Leu Ala Gly
 225 230 235 240

 Met Ala Val Leu Ile Ile Leu Leu Pro Leu Gln Ser Cys Phe Gly Lys
 245 250 255

 Leu Phe Ser Ser Leu Arg Ser Lys Thr Ala Thr Phe Thr Asp Ala Arg
 260 265 270

 Ile Arg Thr Met Asn Glu Val Ile Thr Gly Ile Arg Ile Ile Lys Met
 275 280 285

 Tyr Ala Trp Glu Lys Ser Phe Ser Asn Leu Ile Thr Asn Leu Arg Lys
 290 295 300

 Lys Glu Ile Ser Lys Ile Leu Arg Ser Ser Cys Leu Arg Gly Met Asn
 305 310 315 320

 Leu Ala Ser Phe Phe Ser Ala Ser Lys Ile Ile Val Phe Val Thr Phe
 325 330 335

 Thr Thr Tyr Val Leu Leu Gly Ser Val Ile Thr Ala Ser Arg Val Phe
 340 345 350

 Val Ala Val Thr Leu Tyr Gly Ala Val Arg Leu Thr Val Thr Leu Phe
 355 360 365

 Phe Pro Ser Ala Ile Glu Arg Val Ser Glu Ala Ile Val Ser Ile Arg
 370 375 380

 Arg Ile Gln Thr Phe Leu Leu Asp Glu Ile Ser Gln Arg Asn Arg
 385 390 395 400

 Gln Leu Pro Ser Asp Gly Lys Lys Met Val His Val Gln Asp Phe Thr
 405 410 415

 Ala Phe Trp Asp Lys Ala Ser Glu Thr Pro Thr Leu Gln Gly Leu Ser
 420 425 430

 Phe Thr Val Arg Pro Gly Glu Leu Leu Ala Val Val Gly Pro Val Gly
 435 440 445

Ala Gly Lys Ser Ser Leu Leu Ser Ala Val Leu Gly Glu Leu Ala Pro
 450 455 460

Ser His Gly Leu Val Ser Val His Gly Arg Ile Ala Tyr Val Ser Gln
 465 470 475 480

Gln Pro Trp Val Phe Ser Gly Thr Leu Arg Ser Asn Ile Leu Phe Gly
 485 490 495

Lys Lys Tyr Glu Lys Glu Arg Tyr Glu Lys Val Ile Lys Ala Cys Ala
 500 505 510

Leu Lys Lys Asp Leu Gln Leu Leu Glu Asp Gly Asp Leu Thr Val Ile
 515 520 525

Gly Asp Arg Gly Thr Thr Leu Ser Gly Gly Gln Lys Ala Arg Val Asn
 530 535 540

Leu Ala Arg Ala Val Tyr Gln Asp Ala Asp Ile Tyr Leu Leu Asp Asp
 545 550 555 560

Pro Leu Ser Ala Val Asp Ala Glu Val Ser Arg His Leu Phe Glu Leu
 565 570 575

Cys Ile Cys Gln Ile Leu His Glu Lys Ile Thr Ile Leu Val Thr His
 580 585 590

Gln Leu Gln Tyr Leu Lys Ala Ala Ser Gln Ile Leu Ile Leu Lys Asp
 595 600 605

Gly Lys Met Val Gln Lys Gly Thr Tyr Thr Glu Phe Leu Lys Ser Gly
 610 615 620

Ile Asp Phe Gly Ser Leu Leu Lys Lys Asp Asn Glu Glu Ser Glu Gln
 625 630 635 640

Pro Pro Val Pro Gly Thr Pro Thr Leu Arg Asn Arg Thr Phe Ser Glu
 645 650 655

Ser Ser Val Trp Ser Gln Gln Ser Ser Arg Pro Ser Leu Lys Asp Gly
 660 665 670

Ala Leu Glu Ser Gln Asp Thr Glu Asn Val Pro Val Thr Leu Ser Glu
 675 680 685

Glu Asn Arg Ser Glu Gly Lys Val Gly Phe Gln Ala Tyr Lys Asn Tyr
 690 695 700

Phe Arg Ala Gly Ala His Trp Ile Val Phe Ile Phe Leu Ile Leu Leu
 705 710 715 720

Asn Thr Ala Ala Gln Val Ala Tyr Val Leu Gln Asp Trp Trp Leu Ser
 725 730 735

Tyr Trp Ala Asn Lys Gln Ser Met Leu Asn Val Thr Val Asn Gly Gly
 740 745 750

Gly Asn Val Thr Glu Lys Leu Asp Leu Asn Trp Tyr Leu Gly Ile Tyr
 755 760 765

Ser Gly Leu Thr Val Ala Thr Val Leu Phe Gly Ile Ala Arg Ser Leu
 770 775 780

Leu Val Phe Tyr Val Leu Val Asn Ser Ser Gln Thr Leu His Asn Lys
 785 790 795 800

Met Phe Glu Ser Ile Leu Lys Ala Pro Val Leu Phe Phe Asp Arg Asn
 805 810 815

Pro Ile Gly Arg Ile Leu Asn Arg Phe Ser Lys Asp Ile Gly His Leu
 820 825 830

Asp Asp Leu Leu Pro Leu Thr Phe Leu Asp Phe Ile Gln Thr Leu Leu
 835 840 845

Gln Val Val Gly Val Val Ser Val Ala Val Ala Val Ile Pro Trp Ile
 850 855 860

Ala Ile Pro Leu Val Pro Leu Gly Ile Ile Phe Ile Phe Leu Arg Arg
 865 870 875 880

Tyr Phe Leu Glu Thr Ser Arg Asp Val Lys Arg Leu Glu Ser Thr Thr
 885 - 890 895

Arg Ser Pro Val Phe Ser His Leu Ser Ser Ser Leu Gln Gly Leu Trp
 900 905 910

Thr Ile Arg Ala Tyr Lys Ala Glu Glu Arg Cys Gln Glu Leu Phe Asp
 915 920 925

Ala His Gln Asp Leu His Ser Glu Ala Trp Phe Leu Phe Leu Thr Thr
 930 935 940

Ser Arg Trp Phe Ala Val Arg Leu Asp Ala Ile Cys Ala Met Phe Val
 945 950 955 960

Ile Ile Val Ala Phe Gly Ser Leu Ile Leu Ala Lys Thr Leu Asp Ala
 965 970 975

Gly Gln Val Gly Leu Ala Leu Ser Tyr Ala Leu Thr Leu Met Gly Met
 980 985 990

Phe Gln Trp Cys Val Arg Gln Ser Ala Glu Val Glu Asn Met Met Ile
 995 1000 1005
 Ser Val Glu Arg Val Ile Glu Tyr Thr Asp Leu Glu Lys Glu Ala Pro
 1010 1015 1020
 Trp Glu Tyr Gln Lys Arg Pro Pro Ala Trp Pro His Glu Gly Val
 1025 1030 1035 1040
 Ile Ile Phe Asp Asn Val Asn Phe Met Tyr Ser Pro Gly Gly Pro Leu
 1045 1050 1055
 Val Leu Lys His Leu Thr Ala Leu Ile Lys Ser Gln Glu Lys Val Gly
 1060 1065 1070
 Ile Val Gly Arg Thr Gly Ala Gly Lys Ser Ser Leu Ile Ser Ala Leu
 1075 1080 1085
 Phe Arg Leu Ser Glu Pro Glu Gly Lys Ile Trp Ile Asp Lys Ile Leu
 1090 1095 1100
 Thr Thr Glu Ile Gly Leu His Asp Leu Arg Lys Lys Met Ser Ile Ile
 1105 1110 1115 1120
 Pro Gln Glu Pro Val Leu Phe Thr Gly Thr Met Arg Lys Asn Leu Asp
 1125 1130 1135
 Pro Phe Asn Glu His Thr Asp Glu Glu Leu Trp Asn Ala Leu Gln Glu
 1140 1145 1150
 Val Gln Leu Lys Glu Thr Ile Glu Asp Leu Pro Gly Lys Met Asp Thr
 1155 1160 1165
 Glu Leu Ala Glu Ser Gly Ser Asn Phe Ser Val Gly Gln Arg Gln Leu
 1170 1175 1180
 Val Cys Leu Ala Arg Ala Ile Leu Arg Lys Asn Gln Ile Leu Ile Ile
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 <211> 1262
 <212> PRT
 <213> Homo sapiens
 <400> 538

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Leu Gln Gly Phe Trp Asp Lys Glu Val Leu Arg Ala Glu Asn Asp Ala
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Gln Lys Pro Ser Leu Thr Arg Ala Ile Ile Lys Cys Tyr Trp Lys Ser
 35 40 45

Tyr Leu Val Leu Gly Ile Phe Thr Leu Ile Glu Glu Ser Ala Lys Val
 50 55 60

Ile Gln Pro Ile Phe Leu Gly Lys Ile Ile Asn Tyr Phe Glu Asn Tyr
 65 70 75 80

Asp Pro Met Asp Ser Val Ala Leu Asn Thr Ala Tyr Ala Tyr Ala Thr
 85 90 95

Val Leu Thr Phe Cys Thr Leu Ile Leu Ala Ile Leu His His Leu Tyr
 100 105 110

Phe Tyr His Val Gln Cys Ala Gly Met Arg Leu Arg Val Ala Met Cys
 115 120 125

His Met Ile Tyr Arg Lys Ala Leu Arg Leu Ser Asn Met Ala Met Gly
 130 135 140

Lys Thr Thr Thr Gly Gln Ile Val Asn Leu Leu Ser Asn Asp Val Asn
 145 150 155 160

Lys Phe Asp Gln Val Thr Val Phe Leu His Phe Leu Trp Ala Gly Pro
 165 170 175

Leu Gln Ala Ile Ala Val Thr Ala Leu Leu Trp Met Glu Ile Gly Ile
 180 185 190

Ser Cys Leu Ala Gly Met Ala Val Leu Ile Ile Leu Leu Pro Leu Gln
 195 200 205

Ser Cys Phe Gly Lys Leu Phe Ser Ser Leu Arg Ser Lys Thr Ala Thr
 210 215 220

Phe Thr Asp Ala Arg Ile Arg Thr Met Asn Glu Val Ile Thr Gly Ile
 225 230 235 240

Arg Ile Ile Lys Met Tyr Ala Trp Glu Lys Ser Phe Ser Asn Leu Ile
 245 250 255

Thr Asn Leu Arg Lys Lys Glu Ile Ser Lys Ile Leu Arg Ser Ser Cys
 260 265 270

Leu Arg Gly Met Asn Leu Ala Ser Phe Phe Ser Ala Ser Lys Ile Ile
 275 280 285
 Val Phe Val Thr Phe Thr Tyr Val Leu Leu Gly Ser Val Ile Thr
 290 295 300
 Ala Ser Arg Val Phe Val Ala Val Thr Leu Tyr Gly Ala Val Arg Leu
 305 310 315 320
 Thr Val Thr Leu Phe Phe Pro Ser Ala Ile Glu Arg Val Ser Glu Ala
 325 330 335
 Ile Val Ser Ile Arg Arg Ile Gln Thr Phe Leu Leu Leu Asp Glu Ile
 340 345 350
 Ser Gln Arg Asn Arg Gln Leu Pro Ser Asp Gly Lys Lys Met Val His
 355 360 365
 Val Gln Asp Phe Thr Ala Phe Trp Asp Lys Ala Ser Glu Thr Pro Thr
 370 375 380
 Leu Gln Gly Leu Ser Phe Thr Val Arg Pro Gly Glu Leu Leu Ala Val
 385 390 395 400
 Val Gly Pro Val Gly Ala Gly Lys Ser Ser Leu Leu Ser Ala Val Leu
 405 410 415
 Gly Glu Leu Ala Pro Ser His Gly Leu Val Ser Val His Gly Arg Ile
 420 425 430
 Ala Tyr Val Ser Gln Gln Pro Trp Val Phe Ser Gly Thr Leu Arg Ser
 435 440 445
 Asn Ile Leu Phe Gly Lys Lys Tyr Glu Lys Glu Arg Tyr Glu Lys Val
 450 455 460
 Ile Lys Ala Cys Ala Leu Lys Lys Asp Leu Gln Leu Leu Glu Asp Gly
 465 470 475 480
 Asp Leu Thr Val Ile Gly Asp Arg Gly Thr Thr Leu Ser Gly Gly Gln
 485 490 495
 Lys Ala Arg Val Asn Leu Ala Arg Ala Val Tyr Gln Asp Ala Asp Ile
 500 505 510
 Tyr Leu Leu Asp Asp Pro Leu Ser Ala Val Asp Ala Glu Val Ser Arg
 515 520 525
 His Leu Phe Glu Leu Cys Ile Cys Gln Ile Leu His Glu Lys Ile Thr
 530 535 540

Ile Leu Val Thr His Gln Leu Gln Tyr Leu Lys Ala Ala Ser Gln Ile
 545 550 555 560

Leu Ile Leu Lys Asp Gly Lys Met Val Gln Lys Gly Thr Tyr Thr Glu
 565 570 575

Phe Leu Lys Ser Gly Ile Asp Phe Gly Ser Leu Leu Lys Lys Asp Asn
 580 585 590

Glu Glu Ser Glu Gln Pro Pro Val Pro Gly Thr Pro Thr Leu Arg Asn
 595 600 605

Arg Thr Phe Ser Glu Ser Ser Val Trp Ser Gln Gln Ser Ser Arg Pro
 610 615 620

Ser Leu Lys Asp Gly Ala Leu Glu Ser Gln Asp Thr Glu Asn Val Pro
 625 630 635 640

Val Thr Leu Ser Glu Glu Asn Arg Ser Glu Gly Lys Val Gly Phe Gln
 645 650 655

Ala Tyr Lys Asn Tyr Phe Arg Ala Gly Ala His Trp Ile Val Phe Ile
 660 665 670

Phe Leu Ile Leu Leu Asn Thr Ala Ala Gln Val Ala Tyr Val Leu Gln
 675 680 685

Asp Trp Trp Leu Ser Tyr Trp Ala Asn Lys Gln Ser Met Leu Asn Val
 690 695 700

Thr Val Asn Gly Gly Asn Val Thr Glu Lys Leu Asp Leu Asn Trp
 705 710 715 720

Tyr Leu Gly Ile Tyr Ser Gly Leu Thr Val Ala Thr Val Leu Phe Gly
 725 730 735

Ile Ala Arg Ser Leu Leu Val Phe Tyr Val Leu Val Asn Ser Ser Gln
 740 745 750

Thr Leu His Asn Lys Met Phe Glu Ser Ile Leu Lys Ala Pro Val Leu
 755 760 765

Phe Phe Asp Arg Asn Pro Ile Gly Arg Ile Leu Asn Arg Phe Ser Lys
 770 775 780

Asp Ile Gly His Leu Asp Asp Leu Leu Pro Leu Thr Phe Leu Asp Phe
 785 790 795 800

Ile Gln Thr Leu Leu Gln Val Val Gly Val Val Ser Val Ala Val Ala
 805 810 815

Val Ile Pro Trp Ile Ala Ile Pro Leu Val Pro Leu Gly Ile Ile Phe			
820	825	830	
Ile Phe Leu Arg Arg Tyr Phe Leu Glu Thr Ser Arg Asp Val Lys Arg			
835	840	845	
Leu Glu Ser Thr Thr Arg Ser Pro Val Phe Ser His Leu Ser Ser Ser			
850	855	860	
Leu Gln Gly Leu Trp Thr Ile Arg Ala Tyr Lys Ala Glu Glu Arg Cys			
865	870	875	880
Gln Glu Leu Phe Asp Ala His Gln Asp Leu His Ser Glu Ala Trp Phe			
885	890	895	
Leu Phe Leu Thr Thr Ser Arg Trp Phe Ala Val Arg Leu Asp Ala Ile			
900	905	910	
Cys Ala Met Phe Val Ile Ile Val Ala Phe Gly Ser Leu Ile Leu Ala			
915	920	925	
Lys Thr Leu Asp Ala Gly Gln Val Gly Leu Ala Leu Ser Tyr Ala Leu			
930	935	940	
Thr Leu Met Gly Met Phe Gln Trp Cys Val Arg Gln Ser Ala Glu Val			
945	950	955	960
Glu Asn Met Met Ile Ser Val Glu Arg Val Ile Glu Tyr Thr Asp Leu			
965	970	975	
Glu Lys Glu Ala Pro Trp Glu Tyr Gln Lys Arg Pro Pro Pro Ala Trp			
980	985	990	
Pro His Glu Gly Val Ile Ile Phe Asp Asn Val Asn Phe Met Tyr Ser			
995	1000	1005	
Pro Gly Gly Pro Leu Val Leu Lys His Leu Thr Ala Leu Ile Lys Ser			
1010	1015	1020	
Gln Glu Lys Val Gly Ile Val Gly Arg Thr Gly Ala Gly Lys Ser Ser			
1025	1030	1035	1040
Leu Ile Ser Ala Leu Phe Arg Leu Ser Glu Pro Glu Gly Lys Ile Trp			
1045	1050	1055	
Ile Asp Lys Ile Leu Thr Thr Glu Ile Gly Leu His Asp Leu Arg Lys			
1060	1065	1070	
Lys Met Ser Ile Ile Pro Gln Glu Pro Val Leu Phe Thr Gly Thr Met			
1075	1080	1085	

Arg Lys Asn Leu Asp Pro Phe Asn Glu His Thr Asp Glu Glu Leu Trp
 1090 1095 1100

Asn Ala Leu Gln Glu Val Gln Leu Lys Glu Thr Ile Glu Asp Leu Pro
 1105 1110 1115 1120

Gly Lys Met Asp Thr Glu Leu Ala Glu Ser Gly Ser Asn Phe Ser Val
 1125 1130 1135

Gly Gln Arg Gln Leu Val Cys Leu Ala Arg Ala Ile Leu Arg Lys Asn
 1140 1145 1150

Gln Ile Leu Ile Ile Asp Glu Ala Thr Ala Asn Val Asp Pro Arg Thr
 1155 1160 1165

Asp Glu Leu Ile Gln Lys Lys Ile Arg Glu Lys Phe Ala His Cys Thr
 1170 1175 1180

Val Leu Thr Ile Ala His Arg Leu Asn Thr Ile Ile Asp Ser Asp Lys
 1185 1190 1195 1200

Ile Met Val Leu Asp Ser Gly Arg Leu Lys Glu Tyr Asp Glu Pro Tyr
 1205 1210 1215

Val Leu Leu Gln Asn Lys Glu Ser Leu Phe Tyr Lys Met Val Gln Gln
 1220 1225 1230

Leu Gly Lys Ala Glu Ala Ala Ala Leu Thr Glu Thr Ala Lys Gln Arg
 1235 1240 1245

Trp Gly Phe Thr Met Leu Ala Arg Leu Val Ser Asn Ser
 1250 1255 1260

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<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 539

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<210> 540

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

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<210> 541
<211> 14
<212> PRT
<213> Homo sapiens

<400> 541
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5 10

<210> 542
<211> 15
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<400> 542
Thr Gln Val Val Phe Asp Lys Ser Asp Leu Ala Lys Tyr Ser Ala
5 10 15

<210> 543
<211> 12
<212> PRT
<213> Homo sapiens

<400> 543
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5 10

<210> 544
<211> 18
<212> PRT
<213> Homo sapiens

<400> 544
Thr Tyr Val Pro Pro Leu Leu Leu Glu Val Gly Val Glu Glu Lys Phe
5 10 15

Met Thr

<210> 545
<211> 18

<212> PRT
<213> Homo sapiens

<400> 545
Met Asp Arg Leu Val Gln Arg Phe Gly Thr Arg Ala Val Tyr Leu Ala
5 10 15

Ser Val

<210> 546
<211> 29
<212> PRT
<213> Homo sapiens

<400> 546
Phe Val Gly Glu Gly Leu Tyr Gln Gly Val Pro Arg Ala Glu Pro Gly
5 10 15
Thr Glu Ala Arg Arg His Tyr Asp Glu Gly Val Arg Met
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<210> 547
<211> 58
<212> PRT
<213> Homo sapiens

<400> 547
Val Ala Glu Glu Ala Ala Leu Gly Pro Thr Glu Pro Ala Glu Gly Leu
5 10 15

Ser Ala Pro Ser Leu Ser Pro His Cys Cys Pro Cys Arg Ala Arg Leu
20 25 30

Ala Phe Arg Asn Leu Gly Ala Leu Leu Pro Arg Leu His Gln Leu Cys
35 40 45

Cys Arg Met Pro Arg Thr Leu Arg Arg Leu
50 55

<210> 548
<211> 18
<212> PRT
<213> Homo sapiens

<400> 548
Ile Asp Trp Asp Thr Ser Ala Leu Ala Pro Tyr Leu Gly Thr Gln Glu
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Glu Cys

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<210> 549
<211> 18
<212> PRT
<213> Homo sapiens

<400> 549
Leu Glu Ala Leu Leu Ser Asp Leu Phe Arg Asp Pro Asp His Cys Arg
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Gln Ala

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<210> 550
<211> 14
<212> PRT
<213> Homo sapiens

<400> 550
Ser Asp His Trp Arg Gly Arg Tyr Gly Arg Arg Arg Pro Phe
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<210> 551
<211> 15
<212> PRT
<213> Artificial Sequence

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<220>
<223> Made in a lab

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<400> 551
Phe Asp Lys Ser Asp Leu Ala Lys Tyr Ser Ala

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<210> 552
<211> 2577
<212> DNA
<213> Homo sapiens

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<210> 553

<211> 58

<212> PRT

<213> Homo sapiens

<400> 553

Ser Ile Cys Asn Met Thr Cys Ala Ser Val Phe Phe Cys Asp Gln Lys

5

10

15

Phe Leu Thr Phe Ser Phe Leu Ser Met Val Glu Pro Pro Arg Ala Gly

20

25

30

Val Leu Asn Ser Gln Ala Thr Asp Ser Tyr Gln Ser Thr Asp Tyr Tyr
 35 40 45

Glu Pro His His Thr Gly Gly Glu His
 50 55

<210> 554
<211> 59
<212> PRT
<213> Homo sapiens

<400> 554
Leu Gln Lys Asn Lys Leu Arg Ala Ser Thr Asp Ser Thr Leu Trp Ile
 5 10 15

Cys Ala Ala Glu Ala Ser Thr Lys Pro Tyr Phe Tyr Thr Cys Leu Val
 20 25 30

Met Leu His Gly Gln Gly Leu Ala Leu Leu Ser Pro Thr Asn Leu Pro
 35 40 45

Glu Ile Leu Arg Phe Leu Phe Asn Gly Phe Leu
 50 55

<210> 555
<211> 71
<212> PRT
<213> Homo sapiens

<400> 555
Leu Gly Arg Phe Ser Leu Ser Cys Lys Ser Gly His Ser Arg Gly Gln
 5 10 15

Pro Gln Leu Gly Ala Thr Ala Gln Gly Lys Val His Met Gly Leu Ser
 20 25 30

Thr Ala Gln Gly Ser Ile Gln Asp Ile Lys Val Pro His Ser Ile Asp
 35 40 45

Leu Val Ala Lys Lys Lys Gln Thr Leu Ile Ser Phe Cys His Pro
 50 55 60

Ser Asp Pro Leu Glu Leu Leu
 65 70

<210> 556
<211> 81
<212> PRT

<213> Homo sapiens

<400> 556

Asn	His	Pro	Glu	Gln	Gly	Ser	Ser	Thr	Pro	Arg	Pro	Gln	Thr	His	Thr
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Ser	Pro	Arg	Thr	Ile	Met	Asn	His	Thr	Thr	Gln	Glu	Glu	Val	Ser	Thr
				20					25				30		

Arg	Gln	Ala	Lys	Glu	Ala	Ser	Pro	Val	Leu	Thr	Ala	Thr	Arg	His	Gly
						35			40			45			

Ser	Tyr	Tyr	Ser	Leu	Asn	Ser	Ala	Ser	Thr	Gln	Ile	Ser	Asp	Asn	Ile
				50				55			60				

Arg	Asn	Ser	Leu	Glu	His	Glu	Pro	Cys	Cys	Glu	Leu	Pro	Ile	Arg	Arg
					65		70			75			80		

Ile

<210> 557

<211> 54

<212> PRT

<213> Homo sapiens

<400> 557

Ser	Leu	Ser	Ala	Thr	Pro	Leu	Thr	Leu	Trp	Asn	Ser	Ser	Asp	Pro	Leu
					5				10				15		

Glu	Gln	Ala	Tyr	Leu	Ile	Ser	Ala	Arg	Glu	Lys	Thr	Asn	Asn	Gly	Leu
				20					25			30			

Lys	Gly	Ser	Leu	Thr	Met	Lys	Val	Ser	Ala	Asn	Ser	Trp	Leu	Arg	Cys
					35			40			45				

Gly Phe His Ile Arg Phe

50

<210> 558

<211> 77

<212> PRT

<213> Homo sapiens

<220>

<221> VARIANT

<222> (1)...(77)

<223> Xaa = Any amino acid

<400> 558

Asn	Asp	Arg	Asp	Arg	Asn	Ser	Asn	Lys	Val	Ile	Xaa	Lys	Ala	Asn	Leu
5									10					15	

Ile	Tyr	Phe	Thr	Asn	Leu	Thr	Ser	Cys	Leu	Ser	Val	Gln	Asn	Gln	Thr
									25					30	

Phe	Thr	Cys	Thr	Lys	Arg	His	Lys	His	Leu	Gln	Cys	Ser	Ser	Val	His
35									40				45		

Leu	Cys	Lys	Ile	Pro	Pro	Arg	Leu	Lys	Gly	Arg	Asp	Lys	Lys	Lys	Lys
50									55			60			

Pro	Ser	Tyr	Leu	Ser	Gly	Val	Leu	His	Ser	Arg	Ser	Tyr			
65									70			75			

<210> 559

<211> 50

<212> PRT

<213> Homo sapiens

<400> 559

Thr	Leu	Pro	Pro	Leu	Arg	Ser	Val	Ile	Thr	Leu	Glu	Thr	His	Trp	Ser
								5		10			15		

Thr	Asn	Pro	Val	Val	Asn	Cys	Leu	Ser	Glu	Gly	Ser	Arg	Leu	Cys	Ala
								20		25			30		

Ser	Tyr	Glu	Asn	Leu	Met	Pro	Asp	Asp	Leu	Ser	Leu	Ser	His	Phe	Ala
								35		40		45			

Pro Arg

50

<210> 560

<211> 56

<212> PRT

<213> Homo sapiens

<400> 560

Ile	Gly	Ser	Leu	Lys	Gly	Pro	Thr	Thr	Ala	Gly	Ser	His	Cys	Ser	Gly
								5		10			15		

Glu	Gly	Ser	Tyr	Gly	Thr	Phe	Tyr	Cys	Pro	Arg	Phe	Tyr	Thr	Gly	Tyr
								20		25		30			

Lys	Gly	Ala	Ser	Gln	Tyr	Arg	Ser	Gly	Ser	Lys	Glu	Glu	Glu	Thr	Asn
								35		40		45			

Thr Asp Leu Phe Leu Pro Pro Leu
 50 55

<210> 561
 <211> 57
 <212> PRT
 <213> Homo sapiens

<220>
 <221> VARIANT
 <222> (1)...(57)
 <223> Xaa = Any amino acid

<400> 561
 Val Leu His Leu Asp Gln Met Asn Asn Val Gly Ile Xaa Met Asp Lys
 5 10 15

Gly Leu Lys Ser Pro Glu Ile Lys Asn Pro Ala Pro Thr Gly Thr Ser
 20 25 30

Asn Leu Ser Cys Phe Leu Ser Xaa Phe Trp Leu Met Gln Gly Thr Asn
 35 40 45

Ser Leu Pro Arg Glu Asn Tyr Leu Asn
 50 55

<210> 562
 <211> 59
 <212> PRT
 <213> Homo sapiens

<220>
 <221> VARIANT
 <222> (1)...(59)
 <223> Xaa = Any amino acid

<400> 562
 Asp Leu Tyr Pro Xaa Arg Ser Gln His Cys Ser Phe Asp Pro Ser Val
 5 10 15

Ala Pro Met His Gly Ile Lys Asn Ser Ile Thr Ser Leu Ile Phe Leu
 20 25 30

Ile Ser Tyr Leu Xaa Leu Glu Met Ser Ser Leu Ser Glu Ser Leu Val
 35 40 45

Leu Ser Ser Gly Asp Tyr Val Leu Asp Thr Pro
 50 55

<210> 563

<211> 79

<212> PRT

<213> Homo sapiens

<400> 563

Cys	Phe	Leu	Phe	Pro	Tyr	Leu	Trp	Leu	Tyr	Ala	Gln	Pro	Leu	Phe	Pro
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Lys	Gln	Gln	Pro	Pro	Ala	Leu	Ala	Pro	Gly	His	Pro	Asp	Phe	Ile	His
20								25						30	

Thr	Gln	Asn	Glu	Gln	Ile	Asp	Pro	Ser	Pro	His	Ile	Gln	Asn	Leu	Met
35						40						45			

Trp	Asn	Pro	His	Leu	Ser	Gln	Glu	Leu	Ala	Glu	Thr	Phe	Met	Val	Arg
50						55				60					

Asp	Pro	Leu	Arg	Pro	Leu	Leu	Val	Phe	Ser	Leu	Ala	Asp	Ile	Arg
65						70					75			

<210> 564

<211> 64

<212> PRT

<213> Homo sapiens

<400> 564

Ala	Cys	Ser	Lys	Gly	Ser	Glu	Glu	Phe	Gln	Arg	Val	Arg	Gly	Val	Ala
5								10					15		

Glu	Arg	Asp	Gln	Cys	Leu	Phe	Leu	Leu	Cys	Tyr	Gln	Ile	Tyr	Thr
20							25					30		

Val	Arg	His	Leu	Tyr	Ile	Leu	Tyr	Arg	Thr	Leu	Gly	Ser	Arg	Lys	Ser
35							40				45				

His	Met	Asn	Leu	Pro	Leu	Ser	Ser	Gly	Ser	Gln	Leu	Trp	Leu	Ala	Pro
50							55				60				

<210> 565

<211> 57

<212> PRT

<213> Homo sapiens

<220>

<221> VARIANT

<222> (1)...(57)

<223> Xaa = Any amino acid

<400> 565

Leu	Tyr	Tyr	Cys	Ser	Tyr	Leu	Cys	His	Phe	Arg	Thr	Ala	Leu	Ile	Leu
5									10						15

Ala	Val	Cys	Cys	Gly	Ser	Ala	Ser	Ile	Val	Ser	Leu	Leu	Leu	Glu	Gln
	20							25						30	

Asn	Ile	Asp	Val	Ser	Ser	Gln	Asp	Leu	Ser	Gly	Gln	Thr	Ala	Arg	Glu
	35						40					45			

Tyr	Ala	Val	Ser	Ser	Xaa	His	Asn	Val							
	50						55								

<210> 566

<211> 55

<212> PRT

<213> Homo sapiens

<400> 566

Ile	Leu	Leu	Glu	Phe	Phe	Arg	Asn	Gln	Arg	Gly	Ser	Leu	Asn	Pro	Arg
	5								10					15	

Lys	Thr	Val	Pro	Phe	Ile	Lys	Ser	Glu	Gly	Gly	Glu	Lys	Lys	Gly	His
	20						25					30			

Cys	Asn	His	Ser	Val	Val	Ser	Ile	Asp	Ser	Ala	Ala	Ala	Leu	Leu	Pro
	35						40					45			

Leu	Lys	Leu	Val	Leu	Leu	Pro									
	50					55									

<210> 567

<211> 51

<212> PRT

<213> Homo sapiens

<400> 567

Tyr	Ser	Asp	Phe	Asp	Val	Phe	Cys	Ser	His	Thr	Tyr	Gly	Tyr	Met	Leu
	5								10					15	

Ser	His	Cys	Ser	Gln	Ser	Ser	Ser	Pro	Leu	Leu	Trp	Pro	Leu	Gly	Ile
	20							25					30		

Leu	Thr	Leu	Ser	Thr	His	Lys	Met	Ser	Lys	Leu	Thr	Leu	Pro	Pro	Ile
	35						40					45			

Phe Arg Thr

50

<210> 568

<211> 75

<212> PRT

<213> Homo sapiens

<400> 568

Lys Val Gly Glu Tyr Ile Leu Gln Ser Leu Leu Arg Ile Arg Lys Ile		
5	10	15

Tyr Val Ala Phe Asn Ser Val Pro Ser Thr Cys Leu Leu Ala Ser Leu		
20	25	30

Thr Glu Thr Pro Val Thr Thr Ile Leu Thr Ile Ile Ile Asn Leu Thr		
35	40	45

Cys Phe Gln His Ala Glu Ser Ser Tyr Leu Phe Tyr Pro Leu Ala Asp		
50	55	60

Phe Leu Leu Gln His Ile Ser Leu Gly Lys Leu		
65	70	75

<210> 569

<211> 4809

<212> DNA

<213> Homo sapiens

<400> 569

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cagtgtctaa ggtatgcgtg ggagcctgca cagcaggagc ggggtcttct ggagacccgc 4320
 atgagatgca aagggcagtg gacaaggagc caagggaggt ggctctagtc acgctggtat 4380
 ggtgccagct tgaggatgct gggcaagtcc cgagccgtct gccttcctag taccacagtt 4440
 accactgtct gttacctcgca gagttcaagt gcttcacgtg agacagctac gagacaggcc 4500
 cctggaaact ggaaaatgcy aagtaaatgt catgcacaat tggttac 4560
 aatcaaaaa accaaatcgat gctaaaccct gggattcat aacgtcttgg gctgtacaaa 4620
 ttgttccttg aaatgactca gagacatttt ctgaattggc ttccatcagc caagcatttc 4680
 ttcagaactg gaaaaatgct ttaaattttgg ctttgtcatg attattaaaaa cactctgtac 4740
 attttttattt attgaaatatta acacattgcc tacttttaa aaattggaaa aagaaaaaaaaa 4800
 aaaaaaaaaa 4809

<210> 570
<211> 951
<212> DNA
<213> Homo sapiens

<400> 570
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 aaaatattgg aattttattc atctaaaaaa ttggaccggc ccttatttac catcttaat 120
 ccattttagt actatgggtg agtacatgaa attgaagtct ggcttaatc ttcagaaagt 180
 tatatatcta ttttatttttta ttttttttag acagagtctc gctgtgtcac ccaggctgga 240
 gtgcgggtgcc acaatcttgg ctcactgcaa cctctgagtc ccaggttcaa gcgatactca 300
 tgcctcggcc tcctgagtag ctgggactac aggctgtcac caccacatct ggctaatctt 360
 tttttgtatt ttttagtagag acggggtttc actgtggctc ccattctctg acctcgtat 420
 ccgcctgcct cccaaagtgc tgggattaca ggcatgagcc accgcacaca gctgggactg 480
 ggttaattttaa aagaaaaaga gtttaatga ctcacagtcc cgcacggctg gagaggcctc 540
 agggaaacttta caatcatggt ggaaggcgaa ggggaagcaa ggcacgtctt acatggtggc 600
 aggagagaac gagtgagggg ggagactgcc acaaactttt ttttttttag acaagagtct 660
 ggccctgttg cccaggctgg agtgcagtgg catgatctca gctcactgca acctctgcct 720
 cacaggttca agcaattctc atgcctcagc ctcccgatca gctgggacca caggtatgca 780
 ccaccacacc tagctaattt ttgttagttt agtagagatg gggtctact atgtgctca 840
 ggctggctta aaactcctgg gctccagcaa tccgcctgccc ttggcctccc aaagtgctgg 900
 ggttacaggc ataagccacc acatccagcc tgccacatac ttttaaacta t 951

<210> 571
<211> 819
<212> DNA
<213> Homo sapiens

<400> 571
 cagcttaaaaa atggtttctt gaaatcagtg attagcattc actcaccagt acccctacta 60
 aggggttaggc actgggttgc actcctggaa atacaggagt acaccagaat ttatttctgc 120
 ttattgcttt tggtgcaaat gccgtggctt catctgagga attctagaat tcagagggtg 180
 tagccctcca ctctgctgtc ttgttatctg ctctcattgc atccgtttaa cctgcattct 240
 gaaagatgtt tctcagggttt ttccttgacg attttctct tttctgattc tgacaatgtt 300
 ttaaatcatt gtactgtggt tattttttctt ctgcattttat tttacccatc ttcccttgc 360
 acttgccta ttgtcttttta atttctgcct gttctttatg gctttcaact tcataaataa 420
 catgtttctt caaatctttt tttgtgaattcc agagaggggcc aggcacgggtg gctcacatct 480
 gtaatcccag cactttgggg aggctgagac ggggtggatca cttgaggtca ggagtttgag 540
 accagcctgg ccaacatggt gaaatcccgt ttcactaaaa atacaaaaat taccaggca 600
 tgggtggcgaaa cgcctgtat cccaggtact cggggaggctg agggaggaga atcgcttgaa 660

cctgggaggc tgagggagga gaatcgcttg aaccgggag gcagaggtt cagtgaaccg 720
 agatcatgtt gctgcactcc agcctggtca acagagcaag actctgcctc aaaaacaaac 780
 aaataaaacaa acaaacaac aaaacagaga gattttgct 819

<210> 572
 <211> 203
 <212> DNA
 <213> Homo sapiens

<400> 572
 tatagaatac tcaagctatg catcaagctt ggtaccgagc tcggatccac tatttacggc 60
 cgccagtgtg ctggaattcg cccttagctc ggatccacta gtccagtgtg gtggaattcc 120
 attgtgttgg gcccaacaca atggagccac cacatccagc ctgccacata cttttaaact 180
 atcaggtctc atgagaactc atg 203

<210> 573
 <211> 132
 <212> PRT
 <213> Homo sapiens

<400> 573
 Met Val Glu Gly Glu Gly Glu Ala Arg His Val Leu His Gly Gly Arg
 5 10 15
 Arg Glu Arg Val Arg Gly Glu Thr Ala Thr Asn Phe Phe Phe Leu Arg
 20 25 30
 Gln Glu Ser Gly Pro Val Ala Gln Ala Gly Val Gln Trp His Asp Leu
 35 40 45
 Ser Ser Leu Gln Pro Leu Pro His Arg Phe Lys Gln Phe Ser Cys Leu
 50 55 60
 Ser Leu Pro His Ser Trp Asp His Arg Tyr Ala Pro Pro His Leu Ala
 65 70 80
 Asn Phe Cys Ser Phe Ser Arg Asp Gly Val Ser Leu Cys Cys Ser Gly
 85 90 95
 Trp Ser Lys Thr Pro Gly Leu Gln Gln Ser Ala Cys Leu Gly Leu Pro
 100 105 110
 Lys Cys Trp Gly Tyr Arg His Lys Pro Pro His Pro Ala Cys His Ile
 115 120 125
 Leu Leu Asn Tyr
 130

<210> 574
 <211> 63

<212> PRT

<213> Homo sapiens

<400> 574

Met	Thr	His	Ser	Ser	Ala	Trp	Leu	Glu	Arg	Pro	Gln	Glu	Thr	Tyr	Asn
5															15

His	Gly	Gly	Arg	Arg	Gly	Ser	Lys	Ala	Arg	Leu	Thr	Trp	Trp	Gln
20														30

Glu	Arg	Thr	Ser	Glu	Gly	Gly	Asp	Cys	His	Lys	Leu	Phe	Phe	Glu
35														45

Thr	Arg	Val	Trp	Pro	Cys	Cys	Pro	Gly	Trp	Ser	Ala	Val	Ala
50													

<210> 575

<211> 77

<212> PRT

<213> Homo sapiens

<400> 575

Met	Val	Lys	Ser	Arg	Phe	Thr	Lys	Asn	Thr	Lys	Ile	Thr	Gln	Ala	Trp
5															15

Trp	Arg	Ala	Pro	Val	Ile	Pro	Gly	Thr	Arg	Glu	Ala	Glu	Gly	Glu
20														30

Ser	Leu	Glu	Pro	Gly	Arg	Leu	Arg	Glu	Glu	Asn	Arg	Leu	Asn	Pro	Gly
35															45

Gly	Arg	Gly	Cys	Ser	Glu	Pro	Arg	Ser	Cys	Cys	Thr	Pro	Ala	Trp
50														

Ser	Thr	Glu	Gln	Asp	Ser	Ala	Ser	Lys	Thr	Asn	Lys
65											

75

<210> 576

<211> 69

<212> PRT

<213> Homo sapiens

<220>

<221> unsure

<222> (42)

<223> Xaa = Any Amino Acid

<400> 576

Met	Leu	Gly	Lys	Ser	Arg	Ala	Val	Cys	Leu	Pro	Ser	Thr	Thr	Val	Thr
-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----

5

10

15

Thr Val Cys Tyr Leu Ala Ser Ser Ser Ala Ser Arg Glu Thr Ala Thr
 20 25 30

Arg Gln Ala Pro Gly Asn Trp Lys Met Xaa Ser Lys Cys His Ala Gln
 35 40 45

Leu Leu Phe Thr Phe Tyr Leu Asn His Phe Tyr Gln Ile Arg Leu Asn
 50 55 60

Pro Gly Tyr Ser
 65

<210> 577

<211> 58

<212> PRT

<213> Homo sapiens

<400> 577

Met Tyr Leu Glu Asn Ser Phe Tyr Cys Gln Met Ile Leu Leu Lys Arg
 5 10 15

Cys Arg Leu Ser Lys Ile Ser Thr Gln Arg Val Val Pro Asp Gly Pro
 20 25 30

Pro Ala Pro Val Pro Gly Ser Phe Pro Met Phe Pro Arg Phe Gly Phe
 35 40 45

Arg Leu Ala Pro Pro Ala Asp Thr Pro
 50 55

<210> 578

<211> 52

<212> PRT

<213> Homo sapiens

<400> 578

Met Gln Leu Ile Tyr Leu Cys Phe Leu Gly Leu Leu Tyr Ile Arg His
 5 10 15

His Asp Ser Gln Ser Phe Val Ile Leu Tyr Tyr Lys Lys Leu Asn Tyr
 20 25 30

Tyr Phe Lys Tyr Gly Gln Ile Arg Ala Phe His Ile Ala Lys Val Tyr
 35 40 45

Gln Pro His
 50

<210> 579

<211> 57

<212> PRT

<213> Homo sapiens

<400> 579

Met His Phe Thr Phe Met Gln Leu Ile Tyr Leu Cys Phe Leu Gly Leu		
5	10	15

Leu Tyr Ile Arg His His Asp Ser Gln Ser Phe Val Ile Leu Tyr Tyr		
20	25	30

Lys Lys Leu Asn Tyr Tyr Phe Lys Tyr Gly Gln Ile Arg Ala Phe His		
35	40	45

Ile Ala Lys Val Tyr Gln Pro His		
50	55	

<210> 580

<211> 68

<212> PRT

<213> Homo sapiens

<400> 580

Met Glu Leu Arg Thr Lys Ala Leu Arg Thr Ala Gln Gln Leu Thr Ser		
5	10	15

Cys Val Thr Ala Leu Lys Ala Ala Gly Pro Pro Leu Thr Phe Trp Lys		
20	25	30

Gly Lys Trp Val Gln Cys Cys Leu Pro Leu Trp Gly Leu Leu Gly Ser		
35	40	45

His Ala Phe Tyr Ile Tyr Ala Val Asp Ile Phe Met Phe Pro Gly Ser		
50	55	60

Phe Ile His

65

<210> 581

<211> 78

<212> PRT

<213> Homo sapiens

<400> 581

Met Leu Glu Val Lys Phe Glu Val Ser Leu Arg Pro Thr Gly Asn Glu		
5	10	15

Thr Ala Gly Gln Thr His Gly Thr Gln Asp Lys Gly Ser Lys Asp Ser
 20 25 30

Thr Ala Ala Asp Ile Leu Cys Asp Ser Leu Glu Ser Ser Arg Pro Ala
 35 40 45

Ala His Ile Leu Glu Gly Lys Met Gly Thr Met Leu Ser Ala Thr Leu
 50 55 60

Gly Pro Ser Trp Val Thr Cys Ile Leu His Leu Cys Ser
 65 70 75

<210> 582

<211> 52

<212> PRT

<213> Homo sapiens

<400> 582

Met Leu Phe Leu Gln Thr Ile Asp Thr Lys Cys Thr Gly Ile Glu Ile
 5 10 15

Asn Arg Asn Trp Ser Lys Val Trp His Thr His Ser His Val Asp Val
 20 25 30

Lys Leu Cys Leu Glu Phe Leu Cys Gly Val Trp Phe Gly Leu Gly Phe
 35 40 45

Leu Gly Val

50

<210> 583

<211> 61

<212> PRT

<213> Homo sapiens

<400> 583

Met Ser Thr Ser Asp Gly Phe Ala Pro Pro Pro Gln Leu Gly Ser Arg
 5 10 15

Cys Ser His Ile Arg Gly Pro Ile Lys Ile Ala Arg Asn Lys Phe Pro
 20 25 30

Arg Thr Leu Thr Ser Gln Glu Leu Arg Arg Phe Ala Glu Tyr Ser Gly
 35 40 45

Met Met Phe Gly Asp Gln Thr Thr Ala Gly Gln Lys
 50 55 60

<210> 584

<211> 77

<212> PRT

<213> Homo sapiens

<400> 584

Met	Cys	Leu	Cys	Ile	Pro	Leu	Gly	Gly	Tyr	Gln	Glu	Leu	Cys	His	Cys
					5					10					15

Met	Ser	Thr	Ser	Asp	Gly	Phe	Ala	Pro	Pro	Pro	Gln	Leu	Gly	Ser	Arg
											20				30

Cys	Ser	His	Ile	Arg	Gly	Pro	Ile	Lys	Ile	Ala	Arg	Asn	Lys	Phe	Pro
										35	40				45

Arg	Thr	Leu	Thr	Ser	Gln	Glu	Leu	Arg	Arg	Phe	Ala	Glu	Tyr	Ser	Gly
										50	55				60

Met	Met	Phe	Gly	Asp	Gln	Thr	Thr	Ala	Gly	Gln	Lys				
										65	70				75

<210> 585

<211> 51

<212> PRT

<213> Homo sapiens

<400> 585

Met	Val	Tyr	Arg	Phe	Gly	Gln	Met	Ser	Asp	Asn	Pro	Phe	Tyr	Ile	Leu
											5	10			15

Ala	Ser	Leu	Gly	Ser	Ser	Ser	Cys	Arg	Asn	Gly	Leu	Ala	Ser	Lys	Trp
											20	25			30

Arg	Gln	Ala	Asp	Pro	Ser	Asp	Gly	Tyr	Met	Glu	Pro	Cys	Phe	Gln	Leu
										35	40				45

Leu Phe

50

<210> 586

<211> 61

<212> PRT

<213> Homo sapiens

<400> 586

Met	Leu	Val	His	Ile	Tyr	Ser	Cys	Cys	Gly	Met	Val	Tyr	Arg	Phe	Gly
											5	10			15

Gln Met Ser Asp Asn Pro Phe Tyr Ile Leu Ala Ser Leu Gly Ser Ser
 20 25 30

Ser Cys Arg Asn Gly Leu Ala Ser Lys Trp Arg Gln Ala Asp Pro Ser
 35 40 45

Asp Gly Tyr Met Glu Pro Cys Phe Gln Leu Leu Phe
 50 55 60

<210> 587

<211> 1408

<212> DNA

<213> Homo sapiens

<400> 587

ctggacactt tgcgaggcgt tttgctggct gctgctgctg cccgtcatgc tactcatcg 60
 agcccggcccg gtgaagctcg ctgcttcctt tacccctta agtgactgccc aaacgcccac 120
 cggctgaaat tgctctggtt atgatgacag agaaaaatgat ctcttcctct gtgacacccaa 180
 cacctgtaaa tttgatgggg aatgtttaag aattggagac actgtgactt gcgtctgtca 240
 gttcaagtgc aacaatgact atgtgcctgt gtgtggctcc aatggggaga gctaccagaa 300
 tgagtgttac ctgcgacagg ctgcatgcaa acagcagagt gagatacttg tggtgtcaga 360
 aggatcatgt gccacagatg caggatcagg atctggagat ggagtccatg aaggctctgg 420
 agaaaactagt caaaaggaga catccacotg tgatattgc cagtttggtg cagaatgtga 480
 cgaagatgcc gaggatgtct ggtgtgtg taatattgc tgttctcaaa ccaacttcaa 540
 tcccctctgc gcttctgtt gaaaatctta tgataatgca tgccaaatca aagaagcatc 600
 gtgtcagaaa caggagaaaa ttgaagtcat gtcttgggt cgatgtcaag ataacacaac 660
 tacaactact aagtctgaag atgggcatta tgcaagaaca gattatgcag agaatgctaa 720
 caaatttagaa gaaagtgccca gagaacacca catacctgt ccggAACATT acaatggctt 780
 ctgcatgcat gggaaagtgtg agcattctat caatatgcag gagccatctt gcaggtgtga 840
 tgctggttat actggacaac actgtgaaaa aaaggactac agtgttctat acgttggcc 900
 cggtcctgtt cgttccatgt atgtcttaat cgcaagctgtt attggaacaa ttcaattgc 960
 tgtcatctgt gtgggtgtcc tctgcac aagaaaatgc cccagaagca acagaattca 1020
 cagacagaag caaaatacag ggcactacag ttcagacaat acaacaagag cgccccac 1080
 gttaatctaa agggagcatg tttcacatgt gctggactac cgagagctt gactacacaa 1140
 tacagtattt tagacaaaag aataagacaa gagatctaca catgttgcct tgcatttg 1200
 gtaatctaca ccaatgaaaa catgtactac agctatattt gattatgtat ggatatattt 1260
 gaaatagttt acattgtctt gatgtttttt ctgtatgtt aataaactat ttatatcaca 1320
 caatawagtt ttttcttcc catgtattt ttatatataa taaatactca gtgtatgagaa 1380
 aaaaaaaaaa aaaaaaaaaa rwmgaccc 1408

<210> 588

<211> 81

<212> PRT

<213> Homo sapiens

<400> 588

Met Pro Gln Lys Gln Gln Asn Ser Gln Thr Glu Ala Lys Tyr Arg Ala
 5 10 15

Leu Gln Phe Arg Gln Tyr Asn Lys Ser Val His Glu Val Asn Leu Lys

20

25

30

Gly Ala Cys Phe Thr Val Ala Gly Leu Pro Arg Ala Trp Thr Thr Gln
 35 40 45

Tyr Ser Ile Ile Asp Lys Arg Ile Arg Gln Glu Ile Tyr Thr Cys Cys
 50 55 60

Leu Ala Phe Val Val Ile Tyr Thr Asn Glu Asn Met Tyr Tyr Ser Tyr
 65 70 75 80

Ile

<210> 589

<211> 157

<212> PRT

<213> Homo sapiens

<400> 589

Met Thr Met Cys Leu Cys Val Ala Pro Met Gly Arg Ala Thr Arg Met
 5 10 15

Ser Val Thr Cys Asp Arg Leu His Ala Asn Ser Arg Val Arg Tyr Leu
 20 25 30

Trp Cys Gln Lys Asp His Val Pro Gln Met Gln Asp Gln Asp Leu Glu
 35 40 45

Met Glu Ser Met Lys Ala Leu Glu Lys Leu Val Lys Arg Arg His Pro
 50 55 60

Pro Val Ile Phe Ala Ser Leu Val Gln Asn Val Thr Lys Met Pro Arg
 65 70 75 80

Met Ser Gly Val Cys Val Ile Leu Thr Val Leu Lys Pro Thr Ser Ile
 85 90 95

Pro Ser Ala Leu Leu Met Gly Asn Leu Met Ile Met His Ala Lys Ser
 100 105 110

Lys Lys His Arg Val Arg Asn Arg Arg Lys Leu Lys Ser Cys Leu Trp
 115 120 125

Val Asp Val Lys Ile Thr Gln Leu Gln Leu Leu Ser Leu Lys Met Gly
 130 135 140

Ile Met Gln Glu Gln Ile Met Gln Arg Met Leu Thr Asn
 145 150 155

<210> 590

<211> 347

<212> PRT

<213> Homo sapiens

<400> 590

Met	Leu	Leu	Ile	Val	Ala	Arg	Pro	Val	Lys	Leu	Ala	Ala	Phe	Pro	Thr
5								10						15	

Ser	Leu	Ser	Asp	Cys	Gln	Thr	Pro	Thr	Gly	Trp	Asn	Cys	Ser	Gly	Tyr
20								25					30		

Asp	Asp	Arg	Glu	Asn	Asp	Leu	Phe	Leu	Cys	Asp	Thr	Asn	Thr	Cys	Lys
35								40				45			

Phe	Asp	Gly	Glu	Cys	Leu	Arg	Ile	Gly	Asp	Thr	Val	Thr	Cys	Val	Cys
50								55				60			

Gln	Phe	Lys	Cys	Asn	Asn	Asp	Tyr	Val	Pro	Val	Cys	Gly	Ser	Asn	Gly
65								70			75		80		

Glu	Ser	Tyr	Gln	Asn	Glu	Cys	Tyr	Leu	Arg	Gln	Ala	Ala	Cys	Lys	Gln
85								90				95			

Gln	Ser	Glu	Ile	Leu	Val	Val	Ser	Glu	Gly	Ser	Cys	Ala	Thr	Asp	Ala
100								105				110			

Gly	Ser	Gly	Ser	Gly	Asp	Gly	Val	His	Glu	Gly	Ser	Gly	Glu	Thr	Ser
115								120				125			

Gln	Lys	Glu	Thr	Ser	Thr	Cys	Asp	Ile	Cys	Gln	Phe	Gly	Ala	Glu	Cys
130								135			140				

Asp	Glu	Asp	Ala	Glu	Asp	Val	Trp	Cys	Val	Cys	Asn	Ile	Asp	Cys	Ser
145								150			155		160		

Gln	Thr	Asn	Phe	Asn	Pro	Leu	Cys	Ala	Ser	Asp	Gly	Lys	Ser	Tyr	Asp
165								170				175			

Asn	Ala	Cys	Gln	Ile	Lys	Glu	Ala	Ser	Cys	Gln	Lys	Gln	Glu	Lys	Ile
180								185				190			

Glu	Val	Met	Ser	Leu	Gly	Arg	Cys	Gln	Asp	Asn	Thr	Thr	Thr	Thr	Thr
195								200			205				

Lys	Ser	Glu	Asp	Gly	His	Tyr	Ala	Arg	Thr	Asp	Tyr	Ala	Glu	Asn	Ala
210								215			220				

Asn	Lys	Leu	Glu	Glu	Ser	Ala	Arg	Glu	His	His	Ile	Pro	Cys	Pro	Glu
225								230			235		240		

His Tyr Asn Gly Phe Cys Met His Gly Lys Cys Glu His Ser Ile Asn
 245 250 255

Met Gln Glu Pro Ser Cys Arg Cys Asp Ala Gly Tyr Thr Gly Gln His
 260 265 270

Cys Glu Lys Lys Asp Tyr Ser Val Leu Tyr Val Val Pro Gly Pro Val
 275 280 285

Arg Phe Gln Tyr Val Leu Ile Ala Ala Val Ile Gly Thr Ile Gln Ile
 290 295 300

Ala Val Ile Cys Val Val Val Leu Cys Ile Thr Arg Lys Cys Pro Arg
 305 310 315 320

Ser Asn Arg Ile His Arg Gln Lys Gln Asn Thr Gly His Tyr Ser Ser
 325 330 335

Asp Asn Thr Thr Arg Ala Ser Thr Arg Leu Ile
 340 345

<210> 591

<211> 565

<212> DNA

<213> Homo sapien

<400> 591

actaaagcaa atgaacaagg	tgacttgcta gtatcatctg	cattcattga agcacaagaa	60
cttcatgcct tgactcatgt	aatatcaata ggataaaaaa	ataaatttga tatcacatgg	120
aaacagacaa aaaatattgt	acaacattgc acccagtgtc	agattctaca cctggccact	180
caggaagcaa gagttaatcc	cagaggtctta tgcctaatg	tgttatggca aatggatgtc	240
atgcacgtac cttcatttgg	aaaattgtca tttgtccatg	tgacagtgtt tacttattca	300
catttcatat gggcaacctg	ccagacagga gaaagtactt	cccattgtt aagacattta	360
ttatcttgtt ttccctgtcat	gggagttcca gaaaaagtta	aaacagacaa tgggccaggt	420
tactgttagta aagcatttca	aaaattctta aatcagtggaa	aaattacaca tacaatagga	480
attctctata attcccaagg	acaggccata attgaaggaa	ctaataagaac actcaaagct	540
caattggta aacaaaaaaaaa	aaaaaa		565

<210> 592

<211> 188

<212> PRT

<213> Homo sapien

<400> 592

Thr Lys Ala Asn Glu Gln Ala Asp Leu Leu Val Ser Ser Ala Phe Ile			
1	5	10	15
Glu Ala Gln Glu Leu His Ala Leu Thr His Val Asn Ala Ile Gly Leu			
20	25	30	

Lys Asn Lys Phe Asp Ile Thr Trp Lys Gln Thr Lys Asn Ile Val Gln
 35 40 45
 His Cys Thr Gln Cys Gln Ile Leu His Leu Ala Thr Gln Glu Ala Arg
 50 55 60
 Val Asn Pro Arg Gly Leu Cys Pro Asn Val Leu Trp Gln Met Asp Val
 65 70 75 80
 Met His Val Pro Ser Phe Gly Lys Leu Ser Phe Val His Val Thr Val
 85 90 95
 Asp Thr Tyr Ser His Phe Ile Trp Ala Thr Cys Gln Thr Gly Glu Ser
 100 105 110
 Thr Ser His Val Lys Arg His Leu Leu Ser Cys Phe Pro Val Met Gly
 115 120 125
 Val Pro Glu Lys Val Lys Thr Asp Asn Gly Pro Gly Tyr Cys Ser Lys
 130 135 140
 Ala Phe Gln Lys Phe Leu Asn Gln Trp Lys Ile Thr His Thr Ile Gly
 145 150 155 160
 Ile Leu Tyr Asn Ser Gln Gly Gln Ala Ile Ile Glu Gly Thr Asn Arg
 165 170 175
 Thr Leu Lys Ala Gln Leu Val Lys Gln Lys Lys Lys
 180 185

<210> 593
<211> 271
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1) ... (271)
<223> n = A,T,C or G

<400> 593
actttatgtt cnagtgcana aanccncctg gattgccacc ntactctcag ggctgtgant 60
tgtgcnccca nagcaacctg ggcacgcggg gacagggggg ccnacaattg agggagcggt 120
gtccctagct ggggtctata catgnncngg naaggcngc tgagtnccat nagcaaagga 180
nctagnatnt gcgggggtgc ggcctggcc tacccttta agcatccntn gatccactcc 240
angaaancng gggtagncag gtttnccaaac a 271

<210> 594
<211> 376
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1) ... (376)
<223> n = A,T,C or G

<400> 594
cctttggggg nggggggaac cttaaccatt gtncctttt atttcatggt gttngggttc 60
gcgcctcnngggcaacaa agttatcgtn nttgaagaga anattttttt ggnttngncc 120

cgattaagcg ncaaatgtgt agcaaaaangc cgtgccactt gtggcgtac tncgtcgggt	180
cgattcgacg acaaggcgtn ggcgcgtanc gttagtctcn aatngaccn gtggcatgag	240
cccacgangg ntccgtgtcg tcacatggnc tctagacata acgcncncn tttttncag	300
agggggntgc cgcccttagg gaggnagggg tggggacact agccaancca nantctnacc	360
ccattgaaga aaaggn	376
<210> 595	
<211> 242	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1)...(242)	
<223> n = A,T,C or G	
<400> 595	
agnctgctgn tcgtncctn tatgtggctt catnntgagg acaanagtn cactgaggct	60
tgngnatgcc aggcaaggnc aagctggctc aaaaagcatc cacccaccc tgnnaangggt	120
atgccangag cangtgcacc agtcccaact angagnccn ggcatgntac atcttcttcc	180
acccctnaaa ntggngcta caangnccat ttttctttt ctcttaaggg ncncntggct	240
tc	242
<210> 596	
<211> 535	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1)...(535)	
<223> n = A,T,C or G	
<400> 596	
accagttgga tactgctaaa nagatattta tgccgcctca tatgttaagt cgtatatttt	60
gaaagctttt taaatttttt cttaagaag atttagatg cttatcactg agtaccagag	120
ggatgttaggc tggatgcctt atcaacaaag tcagggactg tggcacacaa ggattgacta	180
ctgcagacac ggccacaatg ctacccctag agggcctgaa tccccctgcc ctctctggtg	240
gggagaaggg ctggcagagc cattagcatg ggctccggcc aatcctggcc actttgacac	300
tcctgggtgt gaccagggt cctggagaa gggatgaggt gggcagtaga gatgctcagg	360
gcagtggccc cttccatcc acactggaa tattcagta ttttaccacc aattcagcca	420
ttcccttgtg cgctggctga acatcagccc tgctccaggt ctcagttcc cctttgtaaa	480
gggaaagctc tggattcagg gagtgatgaa gaggtcatca tggcttgag aattc	535
<210> 597	
<211> 257	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	

<222> (1)...(257)
<223> n = A,T,C or G

<400> 597
tttcnataacc caaaaantacc ccatattang accanacatt tgtctnggaa aaattaccat
tntntaacnt ttgggccacc tgagannaaa tgggtgtaat ncatgataag atggancagn
attnctctta agatnngatn agaccccggtt tttcacggaa catatccaag nacccaataag
gnaacaagcc acgggnggag tcacaaacat atattcttta ctctcataat ccgtnncaca
naactnttg acttgac 60
120
180
240
257

<210> 598
<211> 222
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(222)
<223> n = A,T,C or G

<400> 598
nntggntacc gtcnaaactt nncttggtag ccgagctcggt atccactagt ccagtgtgg
ggaattccat tgggttgggc tataagctgt aatagtggag ncgtgctngg ttcattgcan
nagnccctcc gcanncacnc ttgnnacaac ctgtgagnag gcnataaaatt attcacataaa
tcatcaactgc atgaanctga ctcaaacgca tccacntaca cc 60
120
180
222

<210> 599
<211> 238
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(238)
<223> n = A,T,C or G

<400> 599
gcatgacatc ancgatgtnt ttgggnacct ganatngct aaaactngng natgccgggn
atgnagggtt ggtantgate tatgcactca catctcatgg ggacgttca tgtggagtg
tcgacaangt tgctgnancn gagaagtgtat gatctcagtt gaaagggtca tgtgaataaca
cnttacactt gaaaaagaag cacattggaa atatcacgaa acgnccacca acatcctg 60
120
180
238

<210> 600
<211> 232
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(232)
<223> n = A,T,C or G

<400> 600	
cgaactattt agactaccta gaaaaattat ttttagtatca gaagaatatac aggggtgtag	60
tactcatcg agctaaatga gagcgctta aaaatgttag tttgtcttcc gccatttcta	120
cagaaagctg caatttcagg ttttcaacct aataggtgat atttaaaaaaaa aaaaaaaaaagc	180
aatcgcaaat agccccactg ctttacaaa tcatttttc cccaacacaa tg	232
<210> 601	
<211> 547	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1) ... (547)	
<223> n = A,T,C or G	
<400> 601	
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tttttcttaa atatcaccta ttaggttcaa aacctgaaat tgcagcttcc ttagaaatg	120
gcggaaagaca aactaacatt ttaaagcgc tctcatttag ctctgatgag tactacaccc	180
ctnatattct tctgatacta aaataattt cctagtgtag tctaaacttt tttaaaaaga	240
catgtatccc gcggagttag taactcaaaa cgagtgcattc tnggaagtat cgccgcgtt	300
nctggatnaa attcccagct tgctngctt ctnagccggg gggcggtttaa aaaaacatct	360
gcagcccnngg ggnaaaaacc ttgcattgt tcttacgtgt ttacgttatt ttatccct	420
nnagcaaggc nggganttgg ggactcgaaa tggtagt gggctgggaa tcgcccattgt	480
tacataaaag ncgtccagaa gagggacggt tacaggcngg ganctccaaa ggtcagtccc	540
tgccatt	547
<210> 602	
<211> 826	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1) ... (826)	
<223> n = A,T,C or G	
<400> 602	
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taccattcga gtccctactc ctgccttgc ttagggaaat aaaataacgt aaacacgtaa	120
gaacaatgcg aaagcgccccctt ccctccctagg ctgcagattt tcttcttcc ac cggccctgt	180
tagctagcta gctagctggg aatttaatcc agaaacggct tgcgataacct cctagatgca	240
ctcgaaaaact ccgcggatta catgtctttt taaaaaagtt tagactacac	300
tagggaaaat tatttttagta tcagaagaat atcagggggt gtgtactca tcagagctna	360
atgagagcgc tttaaaaatg ttagttgtc ttccgcatt tctacagaaa gctgcaattt	420
caggaaaaatc ncctaataagg tgatatntaa gaaaaaaaaa acaatcgcan atagccact	480
gcttttacaa atcatttttc tcttcttaggt atagcctgtc aggtggccta atgtatttt	540
gacatctcta ggaattttaa tagaccagaa atgggtgcca gagatatgcc tgcactaatac	600
ttaagtgggg atttatgtat ttctcaanca agtgattaaa gcaaaactag gcacgaatga	660

aatcaagatc	tttaggccag	aatcatgaa	nantttana	attattttan	gaatctgtgg	720
cttctttct	taaaaatngaa	aaaaaaaatg	tttaaaccca	naaggctga	ataaccaagc	780
ncctgaacn	anagaacaan	gccggagcac	cccctccaa	atcccc		826
<210>	603					
<211>	817					
<212>	DNA					
<213>	Homo sapien					
<220>						
<221>	misc_feature					
<222>	(1) ... (817)					
<223>	n = A,T,C or G					
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agtgcaggca	tatctctggc	accatttct	ggttctatta	aaattcctag	agatgtcaaa	240
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gtgttagtcta	aacttttta	aaaagacatg	taatccgcgg	agtttgtaac	tcaaaacgag	540
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tacgtgttta	cgttatttta	tttcctanaa	caaggcngaa	ttgggactcg	aatggttcag	720
ttgggggtggg	ggatcccctg	gtncataaaa	ngtcanaaag	anggtacagg	cggaacncca	780
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<210>	604					
<211>	694					
<212>	DNA					
<213>	Homo sapien					
<220>						
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<222>	(1) ... (694)					
<223>	n = A,T,C or G					
<400>	604					
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aaatcaagat	cttttaggca	anaaaagtcat	gatgagttt	agaattattt	taggactctg	240
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agccaaagca	acactganca	aaaagaacan	agcagggaaag	caacacacta	ccngaattca	360
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ttatcaataa	cnaacaccaa	gaacatatnt	taagggacnt	nctattcaat	aantagtgtct	540
gnnaaaaact	gggaaatcca	tatgcagaaa	naatgaaact	agacccctat	ccctcaccat	600

acgcaaann	caacttcgga	atgggattac	aaaacttaag	acattccaac	ccaagaaaact	660
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<210>	606					
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<220>						
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<222>	(1) ... (263)					
<223>	n = A,T,C or G					
<400>	606					
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tctagtccac	tgtgmtcaaa	ttccattgtg	tggggccnc	tcgcctcg	canagatctg	120
agtgananca	cntgtcccc	ctgaggtgcc	ccacagcn	ttgtnttcag	cangggctna	180
caactcgacc	ggcagcgnan	ggctggcaga	antngcgc	tnnctcattc	ctacgcngtn	240
ngccgcagga	aggangacag	gcc				263
<210>	607					
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<213>	Artificial Sequence					
<220>						
<223>	Primer					

<400> 607
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<210> 608
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer

<400> 608
gataggggtg ctcaggggtt gg 22

<210> 609
<211> 40
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer

<400> 609
gctggacagg gggcaaaagc tggggcagtg aaccatgtgc 40

<210> 610
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer

<400> 610
ctttgtccag atagcccaagt agctgac 27

<210> 611
<211> 46
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer

<400> 611
gatagagaaa accgtccagg ccagtattgt gggaggctgg gagtgc 46

<210> 612
<211> 40
<212> DNA

<213> Artificial Sequence		
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<400> 612		
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<212> DNA		
<213> Artificial Sequence		
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<211> 1350		
<212> DNA		
<213> Homo sapien		
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cagtgggtgc tgtcagccgc acactgtttc cagaactcct acaccatcg gctgggcctg	180	
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gaatccgtgt	ccgagtctga	caccatccgg	agcatcagca	ttgcttcgca	gtgccttacc	360
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gcctcaggt	ggggcagcat	tgaaccagag	gagttcttga	ccccaaagaa	acttcagtgt	1140
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aagttcatgc	tgtgtgctgg	acgctggaca	ggggcaaaa	gctggggcag	tgaaccatgt	1260
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<210> 617

<211> -449

<212> PRT

<213> Homo sapien

<400> 617

Met	His	His	His	His	Ile	Ile	Asn	Gly	Glu	Asp	Cys	Ser	Pro
1					5		10				15		
His	Ser	Gln	Pro	Trp	Gln	Ala	Ala	Leu	Val	Met	Glu	Leu	Phe
						20			25			30	
Cys	Ser	Gly	Val	Leu	Val	His	Pro	Gln	Trp	Val	Leu	Ser	Ala
						35			40			45	
Cys	Phe	Gln	Asn	Ser	Tyr	Thr	Ile	Gly	Leu	Gly	Leu	His	Ser
							50			55		60	
Ala	Asp	Gln	Glu	Pro	Gly	Ser	Gln	Met	Val	Glu	Ala	Ser	Leu
							65			70		75	
Arg	His	Pro	Glu	Tyr	Asn	Arg	Pro	Leu	Leu	Ala	Asn	Asp	Leu
							85			90		95	
Ile	Lys	Leu	Asp	Glu	Ser	Val	Ser	Glu	Ser	Asp	Thr	Ile	Arg
							100			105		110	
Ser	Ile	Ala	Ser	Gln	Cys	Pro	Thr	Ala	Gly	Asn	Ser	Cys	Leu
							115			120		125	
Gly	Trp	Gly	Leu	Leu	Ala	Asn	Gly	Arg	Met	Pro	Thr	Val	Leu
							130			135		140	
Val	Asn	Val	Ser	Val	Val	Ser	Glu	Glu	Val	Cys	Ser	Lys	Leu
							145			150		155	
Pro	Leu	Tyr	His	Pro	Ser	Met	Phe	Cys	Ala	Gly	Gly	Gln	Asp
							165			170		175	
Lys	Asp	Ser	Cys	Asn	Gly	Asp	Ser	Gly	Gly	Pro	Leu	Ile	Cys
							180			185		190	
Tyr	Leu	Gln	Gly	Leu	Val	Ser	Phe	Gly	Lys	Ala	Pro	Cys	Gly
							195			200		205	

	195	200	205
Gly Val Pro Gly Val Tyr Thr Asn Leu Cys Lys Phe Thr Glu Trp Ile			
210	215	220	
Glu Lys Thr Val Gln Ala Ser Ile Val Gly Gly Trp Glu Cys Glu Lys			
225	230	235	240
His Ser Gln Pro Trp Gln Val Leu Val Ala Ser Arg Gly Arg Ala Val			
245	250	255	
Cys Gly Gly Val Leu Val His Pro Gln Trp Val Leu Thr Ala Ala His			
260	265	270	
Cys Ile Arg Asn Lys Ser Val Ile Leu Leu Gly Arg His Ser Leu Phe			
275	280	285	
His Pro Glu Asp Thr Gly Gln Val Phe Gln Val Ser His Ser Phe Pro			
290	295	300	
His Pro Leu Tyr Asp Met Ser Leu Leu Lys Asn Arg Phe Leu Arg Pro			
305	310	315	320
Gly Asp Asp Ser Ser His Asp Leu Met Leu Leu Arg Leu Ser Glu Pro			
325	330	335	
Ala Glu Leu Thr Asp Ala Val Lys Val Met Asp Leu Pro Thr Gln Glu			
340	345	350	
Pro Ala Leu Gly Thr Thr Cys Tyr Ala Ser Gly Trp Gly Ser Ile Glu			
355	360	365	
Pro Glu Glu Phe Leu Thr Pro Lys Lys Leu Gln Cys Val Asp Leu His			
370	375	380	
Val Ile Ser Asn Asp Val Cys Ala Gln Val His Pro Gln Lys Val Thr			
385	390	395	400
Lys Phe Met Leu Cys Ala Gly Arg Trp Thr Gly Gly Lys Ser Trp Gly			
405	410	415	
Ser Glu Pro Cys Ala Leu Pro Glu Arg Pro Ser Leu Tyr Thr Lys Val			
420	425	430	
Val His Tyr Arg Lys Trp Ile Lys Asp Thr Ile Val Ala Asn Pro Glu			
435	440	445	
Phe			

<210> 618

<211> 385

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(385)

<223> n = A,T,C or G

<400> 618

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ggcngataac agtaccacct gntctggttc ctanccccan gacccttaca gtcttaactgg	240
gacacaaggg cttnaaatca aattgcctat cattaagata tacaanganc ntgagaaaact	300
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<211> 869						
<212> DNA						
<213> Homo sapien						
<220>						
<221> misc_feature						
<222> (1)...(869)						
<223> n = A,T,C or G						
<400> 619						
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gaactctcat	acatatgcca	aaattgatga	gtagataaat	atttcagtag	gtagttacta	180
gctttctgtg	tatgataaa	catatggag	aaattaaaaa	cactaaagta	gactcaatga	240
aagcatagta	tcctatgtat	tcgaaaaa	gaaatgtcta	atgaaggaag	gaaacaatga	300
atgaatgcc	ttattccct	tagagtctg	ggacatggtt	ttgcctgaaa	acttcatgtg	360
aattttat	tttgctcac	attacacc	tcttagactt	atacgataaa	gacataaggc	420
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ttccccaaat	tttgagaca	gatggattt	ccggaaagat	gtgtttagct	ttaatcctg	540
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gggtgaacag	tggaaataact	agggtacatt	ttaaaaatgc	taatgctcg	gcctcgctga	660
agaccaaatt	aatttggaaatc	tctgngggng	gnattgatct	ttttataatc	tttctanang	720
attctaattgg	gcttccaggg	atgaaaacccn	ctgnntggagc	tnggaacacctt	ccttttagttt	780
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tatnntnttt	tggaanggnc	cnaattttt				869
<210> 620						
<211> 339						
<212> DNA						
<213> Homo sapien						
<220>						
<221> misc_feature						
<222> (1)...(339)						
<223> n = A,T,C or G						
<400> 620						
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aagcccgaaag	accactggc	ccccgggtag	cccaagtacc	actggtcctc	ctggctcctg	120
acgctncggg	tcttccctgt	ggcgttagact	gccagctcg	gagacccctc	agcccctccc	180
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agcangatag	cccgcggtt	ccaatctgcg	aaaggaggac	cgccnagccc	gaaatgccna	300
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<210> 621						
<211> 267						
<212> DNA						
<213> Homo sapien						

<220>
<221> misc_feature
<222> (1)...(267)
<223> n = A,T,C or G

<400> 621
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ttcctcggtt cgttagactgc cagttcgga gaccctca gccctccccg cttttctcca 120
ccccaggagg ccatcagtag cgagctactg cctcgccac aacctccag caggatngcc 180
cgcggtttcc aatctgcgaa aggaggaccc cnagccaga aatgcnnnac cnagcgatca 240
ctgccacgcc nagccnacgc ctcgtgc 267

<210> 622
<211> 847
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(847)
<223> n = A,T,C or G

<400> 622
cttangntgt cgactgacgt catgcatgan taaaaggcaga ggtttgggtga aatttatgaa 60
aaataaaaaa ttccggcttg tcctgagggaa gagccactac ttgataactc tacaagagga 120
acagatgtga aggatattcc tttaatttg acaaataaca tacctgggtg tgaggaagaa 180
gatgcattcg aaatatctgt ctcaatgtt ttcgagacat ttccgtaca aaaagaaccc 240
agtctcaaaa atatcatcca tccatactat catccgtact ctgggtccca ggaacatgtt 300
tgccagtcat cttctaagct tcatttacat gaaaataaat tagactgcga caatgataac 360
aaactaggca ttggacatat ttttagtaca gataacaact ttcataatga tgcaagcact 420
aagaaagcaa ggaacccaga agtggttacg gttgaaatga aagaagacca agagtttgat 480
ttgcaaatga caaaaaat gaacccaaaat agtgcacagtgc gcagtacaaa taactataaa 540
agcctgaaac ctaaatttga aaatctgagt tcttaccac cagattctga cagaacatca 600
ggaagtatat ctacatgaag aattacagca agacatgcca aaagtttaag aatgangtca 660
acacatttga aanaagantt ctgggcttg aagaaagaaa atgttccact tcataaagaa 720
ggttggaaaga agaatgggag agcccnngaan ttttgcccn gaaattttcg ggaaccctac 780
tggatgggtc nactgggtgg ccatgaatga ataatggact aatcnncnac ttccctnggg 840
aggaaat 847

<210> 623
<211> 681
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(681)
<223> n = A,T,C or G

<400> 623

aaaactgtac tcgcgcgctg catgtcgaca ctatggatc caaagaatcg gcacgagcga 60
aaangctcan gcagcccgcc tggccgcgc cgctcctccc cccaggaaag ccaangtgga 120
ngctgatgtg gtcgcangag ctcgttccac agcccctcan gtgganctgg ttggccgcg 180
gctgccangg gcggaagtgg gtgtccccan gtctcagccc caaggctgcc cctcacaaag 240
caactgggtt ttgcctccac tgccacccctt ggctccgaac ccgctccctt gctgtggang 300
cccaccgtgg gaatccaggt ccccaggtgg actgcctgcc ttgccttcac tgccactct 360
gcccacactt ccctgcctag anaccggaa ggggctgtgt cggtantggt gcccacctgg 420
atgtggcagc accgactgtg ggggtggacc tggccttgcc gggtgcaaaa gtgggggccc 480
ngggaaaagc acctgaagtgc gcccgtaaaa atccccctt aattttnccc caatttgggg 540
ctcnacaaaa aggaaattgc tgaagccaa ggtaccaagg tcacccctaa ggccagggtg 600
aaaagggtccc aaaattccaa tnccaccnt ttgggcttnc ctcttggAAC cccggcccccc 660
tctcntgaan tttaaaaaaaa n 681

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<210> 624  
<211> 661  
<212> DNA  
<213> Homo sapien
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<220>
<221> misc_feature
<222> (1)...(661)
<223> n = A,T,C or G
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<400> 624
atgggtctta ctgtaccacc gggtgaaaat cgatggccgc ggcgtctaaa tatccgattt
tttttttttt tccttctctg actgtccatg gacaaatgaa actaacttaa tctaactaaa
aaacacaact atatittgaa gattttctat ctgcactcaa ggacactttc cacncgggtt
ttgttacctt ttggcttctgt ctctgaacat gaaattnatc tcaagggtt ngatttctgg
accccttatt cctgctatgg gtttgatatt tcttgggctc cagggccact gttgcattgg
gntgacagnt acctccttagc ccatancctc ctatcttggg aaacaaacct aacaactacg
tgtaccttcc atagatctct gattgagtct cagtatncgc ttgctcatgg gcgattcact
tgaatccgtn attggtgcca acaatcctga ctcatgggnn aatggatcct atcacgttcc
cctgattingc aaccctgtta tacatanatc taatcgata gaatctagcn tnggntatgc
gcggctacgc tattcagggn tgnataactat ngcatggcta cgaancctga tcatgatcna
gggtcatgga ctcttatcag gggggtttggg ccngngcttct ttttcnnacc ttggtaaaac
c

```
<210> 625  
<211> 181  
<212> DNA  
<213> Homo sapien
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```
<400> 625
gcaacaatca gatcatgtta aagtaaatct ccattgccct ggatcacttc aggatttaat
tgtccaagga gagcagggtt ctcctgtcaa aaaaaggtgg ggaaatgttt gagagtaaaa
aatacaaaaat tcaaccggtc gaaaatacac cactccattc agtgctctac ccccataaagc
S
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<210> 626
<211> 181
<212> DNA

<213> Homo sapien

<400> 626

gcaacaatca gatcatgtta aagtaaatct ccattgcctt ggatcacttc aggatttaat	60
tgtccaaggaa gagcagggtt ctcctgtgaa aaaaagggtgg ggaaatgttt gagagtaaaa	120
aatacaaaaat tcaaccggtc gaaaatacacac cactccattc agtgctctac ccccataagc	180
c	181

<210> 627

<211> 813

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1) ... (813)

<223> n = A,T,C or G

<400> 627

accaagctgg agctcgcgcg cctgcaggc gacactagt gatccaaagt gaacgtgaag	60
gtgagcagag gagaacctgc gatggcaaag ttaaaaacaa gaggagatga tggcttggt	120
gtggcacagg atgtaaaaaa aattctccctg tccttaagga gttactgcta ttttagtaat	180
gtgccacttc cctacatagc cttctatgca gaaatgctat atttccactt cacaacccag	240
aacgtgcatt ttattttaca tttagaggag gaacaaacaa ccagaaggca aaaactggtg	300
cattatttt tgcaattctc ttggaaagag ttctttttt acttctgctc agacagcaca	360
caactactgg gaatatattt taatttcaaa tctgtatgtt gacatctggt aactcattt	420
ttgctaataatga agttttcaca ggaaggcagca gtcaccagta gctcatctt ttttcagtt	480
ggcaaagtgt tgtttacctt ttattggcct gcattcggtgt ctcttatcac aggatattta	540
attagaaaac gcaagtagcc taacatagaa nagaaatggg gtggtagata atagtagata	600
gaatggctaa atattttat tacagtatgt taatatact gnaattttag gttaaaaatt	660
atgtaataact caaaaggaat tctcagactg gcgaaacacgc tggncacacg ctntcacagg	720
gcttnanct cctnttgagc tttccccctg ntggacttta gtcttcctt tacncccgna	780
gttnccattn ntaccaatt gtnccggaa ana	813

<210> 628

<211> 646

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1) ... (646)

<223> n = A,T,C or G

<400> 628

tttggnggn ggtgtctcnt ttgggtggac ttttgggtc gtagggcccc aaggccgtta	60
atccccgtaat aacgaaagac gaagaagagt cagaagagt cttctataag gatcgggacg	120
agactacctt agaggaataa aggaaaaaaag cagaggagga agagtggtag aaggagtcag	180
aagaaaccca cacgtcggtc tgaacctgga gccttatcaa aaaggtctag ataaacgata	240
gcgatctcga tatcgagctc aagaggttagg ttttagagact tctcgctc gagagcgaaa	300
tggaagatct cgacgacgat aagaagttaa agttagaggg gtgcttgagg agcgcgtgga	360

aggattctgc ggagggaccc atcgacgtag agacttgaag gcctactaag gtccacaaga	420
agcccggtc tttctccgaa tggtcggagc gtacagtatg cgacgtcgat cggcagacaa	480
gctggcggt aactogaagt gttcgggcga atcgacttat aatagtcgcg cgctagtaac	540
gttaggaacac gaagagttagt cgaaaagaaaa cgtttagtga gggaaaagat tagggaaaaa	600
ggagaggctt aataactaag acacttggag cctaggccaa cgcgaa	646
<210> 629	
<211> 617	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1)...(617)	
<223> n = A,T,C or G	
<400> 629	
ccccccnccc ccctcctngg gcttatnggg acagacccac gtagtactct aaatttctc	60
ctacgcccga caacggaccc tataccaatt cgaatcttgg acactccgac cgccggattc	120
tcttccctt tcggcttccc ctttctgtcg gtaccctcc ctatcgctct cttcacacctt	180
cgtaccgtcg atatatagtc gccgcggact agcctattta ggtgtcctag actcgttatt	240
gatccactca ttagtcttagt actatgcgtc acgtatctta gttgcctaag agggagatta	300
aatcctccac aagttccgac gaattccctgg actctcgtaac tagcaaactt tcttatgagg	360
cttccttgta tatcttctgg atgtttctcg tgtcccggtc ctccgctact actagagctc	420
cttgccttat ctctagaagt agaggactct cgggttcgtt ctccaaatct agcgctagag	480
ctatcgctac ccgctcgatt ccccccagcgg aatcttgaaa cctgaggtag tacacaaacc	540
ctccncatct tccctcggtt gtccttctt ctcatcccc cttcccgct tctcggaaan	600
aatctactt tancttc	617
<210> 630	
<211> 644	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1)...(644)	
<223> n = A,T,C or G	
<400> 630	
cnntcggcnt gggtttntt ctgagnnncc cccccccccc cccccccaaa cttacaccca	60
ccaaacactt tccggccccc acctaggaga cattagaagg gtttaggtt cggcgtatag	120
taaagtccctc tacctcgaa gtagagaatt cggtatTTAA attcagggtt agaggctcgc	180
tcgttagatt tatagtttag gtttagaaatc ggaaaccttc gatcttcctt agaagggtaa	240
taagtggc cctaaatccg tctaaccaag gcgttaaggt ccgtaccta acctagtctt	300
atcttctatc aggccacca atataggtat gttctacttt cgtataggcc ttaaggaata	360
gttcggtagt tatcgaaggc actcctctt aggctaggct tttctcgttc ttagtactcc	420
gggaccgtcg tcgcanaaat atcgatggac ggtaggatc tccgcgtac gcgtcggct	480
aggatatacg agcgaattat cggcgagagg cggtcgtan gaatcggtat caatatgntg	540
ttctttaccc tacggatatc ggcagaaaac ataaaacctt ctnaccangg ataaggatt	600
atcgacccca taaaataaca gtaacattta gantactgtt accc	644

<210> 631
<211> 526
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1) ... (526)
<223> n = A,T,C or G

<400> 631

ccntcggctt	gggtttttt	ctgagcccc	ccccccccc	ccccccccc	cccccccgcc	60
cccatagccc	caccggnccc	acccaaattt	taacaaaata	aatntaccta	tcgnntcacct	120
atcccncgta	tcgngtaggt	cggttaccggt	accgngnac	ncnacgattn	ttcgggtcg	180
cncccttaan	acggncccg	tgccnccgga	anaaatacta	cgagnactc	taatntagca	240
anacccgccc	tcnattanta	gcatttccttag	tcttccaatg	ncgnggattn	ngaatccttn	300
naagttatcg	ggttagaacgg	gtcccggtcc	cccgcctct	ttncaattaa	cgccgggtac	360
aaantcggtt	tctaaattcc	ncacgaattt	ngncggcaac	attcnccgggn	ccttattanc	420
cnttccaac	cccgatacnc	nagctcgatc	gggcatttanc	gaatccgggg	tcncccccga	480
ngantccggg	tcctttgagt	ngctctagga	cggttacgac	ggagga		526

<210> 632
<211> 647
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1) ... (647)
<223> n = A,T,C or G

<400> 632

tttggnggc	ggngctcat	ttgggtggac	ttttgggtc	gttagaacct	ggtatgaggg	60
gtgtttttag	tttcttctc	gtcgctctg	ggaggttcgg	tttcgattga	gattcgggtt	120
cgtcttatac	ttacgaggca	ccctgatatt	gttgcgttt	ggtttgggtt	tggagagttt	180
tgtcctactc	tagcgggtca	tgcggatgtat	atgtagcctg	cgtggcctga	tagtcatgttt	240
gtgagcttga	gaggggagtt	gtgggtgtt	cggcggagtt	aggaggggtt	ggagcacccgg	300
gattgggaga	tatagaatca	taagtgttag	gtataggtcg	attgagcgag	tttgtggat	360
tcgtgtggc	atcataatta	gagtggat	gggcctata	tttcttagag	gacgcacgg	420
cgtgattcgg	ggttttaggg	gtgttcttct	tgtggcaccg	attagctgt	tcatgtatgg	480
aaggaccata	ctgtttcgaa	tgaggattcg	tgtttcgga	ttgttgtgga	tattgtggnc	540
tanactattt	agtgtaaagcc	ggaggtgggtt	tgccgtgggt	gagtatccga	nnttcattcg	600
ganggtatgc	gtgcggagcg	gtcctttag	acatccgga	aaaatgg		647

<210> 633
<211> 630
<212> DNA
<213> Homo sapien

<220>

<221> misc_feature
<222> (1) ... (630)
<223> n = A,T,C or G

<400> 633

tccttcggct	tgggtttttt	tctgacccccc	cccccccccc	ccccctcgga	aggcctctag	60
gctcccaccc	gtctctctaa	tcctcaggaa	ccgatccacc	caaccaactt	actaatgtcc	120
tacagtaaac	acccgagaat	ataaaaccac	acctaggcct	ccaatcctac	caggaaagca	180
agaagccgta	gtctagegta	ttacgaaccc	gagatagaga	cgaggatact	tagtttatt	240
ctctcggaaat	aggaaagacg	actggggagg	aatataggc	tagcgcgggg	ataggggcta	300
tggcggatat	ggggcggggt	cgctctctta	ttcttctata	ccacgtcaat	aggaatgtag	360
atatacctag	atgttcccgt	agaaaagagac	gttagaggtc	tccgaagacta	taaaggagag	420
gcgcgaagaa	acttcgtact	ctagctttat	atagtagtc	gctctagtc	cataagcgac	480
gagagatcta	ctagatttcg	gtatcggcgt	cgtatgtatt	cgaardatgtc	ttcttcccct	540
tttcgatctc	ctctctatac	tacatggnga	ttatagtcnt	aagatagtc	ggatattagg	600
atattagtt	tatgacgttc	gacgggacgg				630

<210> 634
<211> 647
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1) ... (647)
<223> n = A,T,C or G

<400> 634

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caaccctata	gtttactcgt	ataggggaaat	cgaggagaaa	taggaacgaa	gagcgggtga	120
taaagagaaa	gtactttcct	ttatatgtta	agagcttagc	gtaatgactt	tcgttatatg	180
gctagttgat	tttatccggc	tttatagggc	ttagttctgg	ttatctcggg	tctaattccc	240
ttagtagtgc	cgggagttt	acgaggtcac	gggatagcgc	gtacccttc	taagttctt	300
ggaaagctat	tcgttattta	tcgcgattct	cgaggtcgaa	aggatcaagg	atcttccctt	360
ttactaccct	agtcgggtta	gcggtcggc	aaaactagtg	tagtacctt	acccctcgcg	420
agttatagt	cgaaacaacg	tattagtgc	aattatagcg	gatagatcga	gacggttctt	480
tctcgggttc	tcagccggta	atccctctat	ttgggggtct	tctccctt	ccctttgtc	540
ttccgcctta	gcttccaagg	ttcctcgaa	gcgaggggtt	ctacttaagt	cgnatagcggt	600
ccttataaac	cncctacagg	cagacccct	tgtaaacggc	tcgggtt		647

<210> 635
<211> 645
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1) ... (645)
<223> n = A,T,C or G

<400> 635

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agatacccaa	agaatagttc	caactcaactt	cgtctaagta	aaactctaga	acttccaaac	120
ataaaagact	tcgcgcgggtt	agctacacag	cctacggaa	tctcacgaat	cccgattcaa	180
gtcccactct	cgaccacacc	ccggtatcgt	cgtttccca	taccaatgtc	aaaaaataaa	240
ataaaatcca	gtcaagcccc	acggtaaagcg	ggggtagggc	taggcgaaga	ggcaggaacc	300
tttcgaggcc	gggggcttcc	aaaatacaaa	acaactactt	aaagtttacc	ccttctaaag	360
tcggggcaaa	cggttaaagc	acgcctctaa	agtactactc	gtttcgagaa	ggggtagtca	420
tctccgcatt	agagactctc	gcgtatatac	actcgcatcg	tttctagcat	tccgacggtc	480
gcccgcggct	acatatctt	cggatttagt	ccgagggact	atagggttaa	ttagtctagt	540
aaattctctt	agaggatagt	cggggtcgta	gttaggcagt	acgaggggac	atgnctgcg	600
tcgtgctcta	cctgacagc	atactcttat	aaacatcttt	ttcct		645
<210>	636					
<211>	643					
<212>	DNA					
<213>	Homo sapien					
<220>						
<221>	misc_feature					
<222>	(1) ... (643)					
<223>	n = A,T,C or G					
<400>	636					
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cctggctccc	tcctagnggc	tttacgaacg	tccctcctct	tcttacggct	cggaagtgg	180
tacggtaaaa	tccggagggng	gggctaacga	atccaaggct	aactcctctt	anagtttgg	240
gtccncncgt	tttagtaagga	tccgtggagg	gcgagtattt	gnccccggc	ctttattna	300
tagttcccta	gtacgataaaa	gntaccggct	atccattac	agcggataaaa	agttatttan	360
agggccgacg	tcnccgctag	acaggctaca	gctagngggag	gtaccgcctc	cgactantcc	420
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gggacggcag	ttcccnccgtt	tagtgtgcgt	tatagagaag	ggcatttgag	ttggacgtta	540
cnttttaaca	tagtttattc	cgtttaggtt	cttgcgggcc	cgtgggggta	gtncnccggc	600
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<210>	637					
<211>	631					
<212>	DNA					
<213>	Homo sapien					
<220>						
<221>	misc_feature					
<222>	(1) ... (631)					
<223>	n = A,T,C or G					
<400>	637					
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cgctggaaag	actagaagtt	agctacggac	gattagtgt	attccactct	taataacgag	120
taatcgttt	cgtcggtt	gtgtttcggg	gttttggaga	gtaagcgtag	ttgtggagtt	180
tcgcatatag	gtccccttac	tccggcgate	tcgttctctg	tcggttaggt	tattattgtt	240
catccttcgc	attagtagta	gggttggtcg	gataaatcga	tagctattct	ttagaattcg	300

tagtcggaga attcgtgtac gaagtccctt aagttcttta agttcgcgag taagacgtgt	360
acggtttattt tgtcgtcgac gtaggtgtcg tttacgggag tttcgaaaaa ggggtttacg	420
tagaacgtta ttaagcacgg taatacgata gaggattacg cgacgtattc gtcttagaac	480
gtcgattttt cgaaggcgca ttgttatcg aaggggagtc cttggagaat cgagatattc	540
caagaatatt acggagatta cagatcgaa ggctcccgag atcggacgta ttaccggct	600
cgcggaaac gagtaggtat cntccggata a	631
<210> 638	
<211> 606	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1)...(606)	
<223> n = A,T,C or G	
<400> 638	
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taccggcttc cttccgggaa gcacgtcg ggaaaggaa gagagcggtc tagttcgtag	180
gcaaacaggt cagaaaagtt aaggttaaag gtcggagggg agaggatagc tagtacgctt	240
agttcggggc tcgggcgcag ggccacttgc ctcttcgctt ttcctttact ctgtttacga	300
gttcaggctc cggagttccg cgccggaggt cgtcgacg ctaggaatgg ggactcgctc	360
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gttccgtcg taccggccact cgtcgcttgc atccggcccg ctccgcttaa gggcgatgaa	480
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cnncgt	606
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<212> DNA	
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<220>	
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<222> (1)...(592)	
<223> n = A,T,C or G	
<400> 639	
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atcccaccc accgcgggaa gtgggttgcna cgcttagttc tagaatccctc ggaatcgatcc	120
tccggcggtt gtagttccgg cgattccgag tatgccgaag tgtatcgctc cgtctagagg	180
ttggtatctg tttatcgca tgacgctatt gactcgatg ctggtaaagtttggatag	240
gcatatcgat acgcctccgc ggtgtcctct gaagtggccg catccgttgc cgcacgttag	300
acagctctgg tggacgataa cggcttctcg tactctact ccggcttataa tgtagagag	360
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tctaacagtt cttccggcg ctccgaattt agattgacgc ctccgcagca ttgtggatc	480
ctcttcgggtt agccctcttt ataggatttc tcctccggccc cggaaaganggg ctggtcgtcc	540
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<210> 640
<211> 637
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(637)
<223> n = A,T,C or G

<400> 640
ctttgtggcg gtggntgtct catttgggtg gacttttg gtcgtaggct tatccggtn 60
gggctcccgta agtagcttag gatcgccggc tagtccggc cccgccccgtc gaaagcgcgg 120
ttcggcgggc ggcccccggt tcgttcgccgg gcttaccct catagagtgc caggctcg 180
ttcttacggg ttcgtcgccg atagattta cggcgagagg tcggtatctt cgccgcttta 240
cgttcggtcg gcatactacgc ctatgtcaca ggttagttat ggcgcggagc gctgtacgga 300
gagggttatac gggacgcgga agaaccgcct ccaaataact agtacaggct cgttcggtcg 360
tagatctcct cgctcggtcg gcggttctta cttcttagggc cgctctacgg tttaaggcgg 420
tcgttagatc ttagaaaacta tactcaagtt tcagtcggaa gaaaggaagt agagagaagg 480
gtaaacgatt acctccgggtt ctagccctt ttactcgcat aacgggagaa cgggtccgg 540
ctctcagata cgcctcgcgaa gacgtcgca ttcaacttta acctccgcta gggcatccgt 600
atacggttaa cgcggtaaaa ggcacctcgaa aaacctc 637

<210> 641
<211> 649
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(649)
<223> n = A,T,C or G

<400> 641
ctntgtggcg gtggttgtct cagttgggt ggattttgg gtcgtaggna acctggatg 60
aggtctagtt tcttaaacga ttcttgggtc agttacgcga ccctatcctt atttacaat 120
gtcttctaca tcaggttcat caattaatat atcaattaca cattaacgac ggtgtacgc 180
aatatgagaa agtatacatt aaggttatata tatattttc gctaaaaag gttcctgaca 240
tgggacaact tcacccacca ttctagaagc ccccccctt gtaggacccc ctgcagttcc 300
ccattatctt agttagttt tcattttta accaggaggg tatcggttt taataggtac 360
tattttgtca aacttttcag aagctttatc ttcaaatata ctgcaccat ctgtactagg 420
agcactaact attcgagtct attacagctc aacagaaaat aattgaaatt aaacaaccta 480
agtatcgtcc accataaccc catcgccgtc tcacccatt tcttcataag ttctagagca 540
tcctgagctc ttccatattt cccttgcgtgg tactcatggt ctaataccccc ccgcagttat 600
aggtccttat ggatcctatg ctaccacccg tctaattccct tctatcacn 649

<210> 642
<211> 645
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(645)
<223> n = A,T,C or G

<400> 642

tccttcggct	tgggtttttt	ttcgtcgccc	gttactatta	tcgattgtta	cttgtaaagg	60
cgatactccc	accgctcacg	atattagacc	tgctcctcta	gaagcgaacg	gcgataggtc	120
tactcggccg	gcgaagacgg	cgaacgggta	ggaggagcca	tatgcaaccc	taacggagat	180
tataagtact	ggaaaaata	ctagtattaa	ggttagcgggt	taagataggt	ggagagacac	240
tattcacgag	cataaggact	tagaaggctt	tctcgaggag	aggttaggcta	cggactacgt	300
tccttcgtcc	tctagcctcg	agagggagta	tagatgattc	gcaaaaagaga	atccctccta	360
tacgctggca	taactagacg	acgcgtcgtc	gggaaatctc	gccaaaccctt	ttgcgacctc	420
caaaaggaag	attgtcggtt	catagaacgc	taatactccg	ggtcttccc	aatcatagcc	480
gcatatcggt	aagaagacgg	taaaatcgcg	cgattctaac	aagattctgt	agacttaagg	540
ctaagcacta	gaagcgatct	cgattccgga	tcttaagatc	atactaatacg	ttcggtcaca	600
ccagacgacg	attagccact	agaagcccta	ctccgtngaa	accgg		645

<210> 643
<211> 586
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(586)
<223> n = A,T,C or G

<400> 643

ctttgtggcg	gcgggtgtctc	atttgggtgg	attttgggt	cgttaggaacc	tggttatgcag	60
ggtccgcccc	gaattaaaag	cgggatcccc	aaaacgnngn	ttcgcaagaa	gagaagaatc	120
atagcgatag	anctttcata	gtacaaagggt	aactaagagg	aaaataatgc	agattcagaa	180
ctagttgccca	aattagaact	cgatttagggc	aaggatccga	gcctggcgct	atcacttcgg	240
gacttaagct	acggttagagc	agtcggtcct	gaagcatagc	tcccgtagga	cgttagaaac	300
tagtccggca	cggaggacat	actctcgagt	ctcgaacgt	ctattnagaa	tataaacgca	360
ttaacctcag	aaggcccgca	cgcggttact	ctcttagggaa	ctattnattt	ccttccggag	420
ctccccctatt	tttccaacac	atataccggc	aaaggaaaat	cttntgtcct	cggtctaaag	480
agaggaaaaa	aaaacgatat	ctaggttcgg	gtttatccat	ttaaaaanat	ngacgcgact	540
actccctttc	aaaggagtt	tccccctagg	nagagttcaa	cngaag		586

<210> 644
<211> 646
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(646)
<223> n = A,T,C or G

<400> 644

ctttgtggcg	gtgggttgtct	catttgggtg	gcatttttg	gtcgtaggaa	cctggtatng	60
agggctattt	gacttgttcc	tcaaatccca	tggtatggtg	ggtggcgtgc	gggtggcgg	120
tcggttcggc	gggggtgggg	gtcgtcctcc	aaaggagttg	ctagagggct	tttagtggtt	180
ttagggcggg	aaggggtag	agcggagaga	cgtcgtcgt	gaagcttctg	gcccggcgcg	240
agaaggtagt	tagccccgt	tcggaagatt	ctcagaattc	gagaagaggt	agtggggcgc	300
ggagagagag	tttctaagtc	taaacgtaga	ggtcgtccta	gtcgggcgg	gagtagctt	360
taagctagag	gtcgagggtcc	tcgtttaggc	tccgggctct	tcgggcagta	tcctcttct	420
cggagaacgg	agcgaccgac	gtcgtagccg	gaccgtcta	tccgtacgtt	tagagatacg	480
ctcacctcca	cgggcgtata	tgcccgtata	cgtataaacg	cgtaatatac	tcgcgcgtaa	540
aacacgtata	cactatatac	acgcatcgta	cggaccgtat	agcgttatac	gcccgcgtat	600
attaatttac	acttatatac	gcgttaacac	gatatatcac	acnccg		646

<210> 645

<211> 654

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(654)

<223> n = A,T,C or G

<400> 645

nccntcggt	tgggtttttt	tctgacccccc	cccccccccc	cccccggtcg	acaacgtgcc	60
caccgttgcc	atcccagcat	agctggttcg	ttctgtttta	ttcttagtag	tttagttcgc	120
ctatagtcgg	tcgtctatcg	tctatcattt	aaggaggccg	ggctcgctct	ttagggcggg	180
tatcttaggt	attcttctgg	tttcggctgc	cgtctcggag	tctggtcctt	ttgcttct	240
ttcttggtcg	aacttcgtgt	ttgatcgctg	tgtttctttg	gggtgtgtcat	acctaagggc	300
cacttcgcca	acaaaacaagt	ttgtgttagtc	gtttcttattt	gggttcgtcg	gccggcgctc	360
ttactggttt	gcgattttta	acgcgtttgg	ttttaatttgc	tttcctcccc	tagggctcgc	420
tcggctttct	ctctgttcgc	tgctctcgcc	cggcctttgg	tgcggggata	gctccggcta	480
ttancgtgcc	gtgtccgtgt	ggntttgtc	caatgtgaag	gcctaggggt	gcgggcttct	540
ttggccatgg	nttccctct	tgtgancctt	agggtaacg	antcgtaatt	naagggtcggt	600
gttgnata	cgttntangg	gangcctng	tccgntattc	cttgggggttgg	cctn	654

<210> 646

<211> 645

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(645)

<223> n = A,T,C or G

<400> 646

tccttcggct	tgggtttttt	tctgagccccc	cccccccccc	cccccacgcc	aagtacacag	60
acccaccaaa	aacaacgtca	acacaacttc	gggtatacgg	accttaagag	agaccccgta	120
gtagacccta	ccacagccat	ccaatagtca	aacaacaagg	gcccacccaa	tccatccata	180
gagctatcaa	acaacggagg	gaaaggaaa	gagcagggtc	aacttagcag	agatcgaaat	240

cggcactaat tccttcaga tactcgctcg gctttagtt cggggtaaag tccgctctca	300
aaggggccaac gaggtttaa agcgacccc gtatcgagtc ttcttcgtat tcattaaggc	360
gttaaaggta cgagacctag aagagagttag aattagccca ccaaatcgcc taaaccggca	420
aaaacgacca aaagtcaaag acccttacaa atatcacctt aaaacgc当地 cccaaaaaac	480
gcatcgat acgcacgtac ctcccccacg ctttttttc ttcaactctc caaaaacaac	540
ccgaatattt agcgaaaaaa atatccgagg gagaattaga agctattacc cgaaaaaaaaa	600
ncgganangg antaaatngt gggaaatana cgttggttt ttctg	645
<210> 647	
<211> 753	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1) ... (753)	
<223> n = A,T,C or G	
<400> 647	
accttacctg gtaccggcc cccccctcgag tttttttt tccaaataca actcagattg	60
tatacgaaaa gctgataata cattgacttt tgctgtttaa atcccttgag ccttgataa	120
tgatTTTTT tggtaaca attgttagtat ataaaatcggtt attcaccatc cttctgtatgc	180
catattgatt agtttgattt tatggtgatg ggatcattgt gtgttaactg tattaagaag	240
aaatggattt gattgacttt gcatccattt ttatctgtgt tacittcatg ttttattaa	300
aagcatttct ggaccagaat aagttaaatgt gtataatttgc tttttacac gtttatataa	360
ttgaagtttag caatgtggca aaatctctaa tggaaataaa atgcttcaga atgatgacat	420
aaatctgagc tatttcttgc ctggagaaca agtgttattc ataataattt aatagcttct	480
gagggtttt gttcatgtga tgaaggctta tccaccttgt atcaattcat gggctctgct	540
ttgtttaatg tagtcagggtt gttataacna gacttaagag tcatcctact gtgataagt	600
gtgagtgaag attacatgtc ttangaaaat tatactggaa atatctctga cattaatggg	660
tttaaatgtt ttaaggctag gggatgatgc aatganaan atncttccaa angtttctgg	720
ttgtttatat ttngaaagn catnaagana ccg	753
<210> 648	
<211> 383	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1) ... (383)	
<223> n = A,T,C or G	
<400> 648	
gatatcccg ggaaatgcgg aggcccttng gcttacgtgt ttaccgcgtt gggcaaaagcc	60
ttgncaaatt cccggccagc ggagcggcga ggggtgggac tcacggaaag ttaaacagcc	120
tcgtcgccgt cctcgaggct caaaaaccag gctctaggcg gggacgactg cagccgttat	180
ggaggccaccc gggctacgg ccgcggctga ggcctccccca ggtggagcgg tggctggag	240
ggaaatcttg atcctgggcc agccacctgt caagaggagg cggagcgtca tgcctctgga	300
agactggatg aatattctcc aggagcgttca cgaaggcgaa gaagtctttg cagaggaaat	360
tgaatgctgt ctgatgctac aat	383

```

<210> 649
<211> 349
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1) ... (349)
<223> n = A,T,C or G

<400> 649
cgattgtnta cnagtcttag agtaagctta agntcgntac cgagctcgga tccactagtc      60
cagtgtggtg ggaattccat tgtgtgggt cactagtaaa tggathtagc tagacanagg     120
anatttaccc tattccattt agcacagtga gganaggcta nacagctagg atgcaataaa    180
aaaaatttta atgagaaaatg tgtgtggtag attaattcta ttaatctcaa gttatagatt    240
aaaaaatttta agtaccncat aaatgccatt tgcccttgct aangntacat ttttatgaan   300
aangacntg catacnnaat ganatactgg acttnggna cttgangga                  349

<210> 650
<211> 306
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1) ... (306)
<223> n = A,T,C or G

<400> 650
cattgtgttggagcatcct tccatcagct cccatgagaa attctctgtt gggtttaagc      60
aatccccaaa tatatcatat tgacatgaat atatcatctc ctcaatgtcc agcattagca    120
gacaagatga gtgctgaaga tgatataact cctaccttctt atgtaggcta gaggttaaagt  180
ctggctctgc tgactgtggg gacataccga aaaggaatgt gggttaatat cagangacct  240
ccctgcagat ccganantca gggncctggac tttctggan aggaagcnna aagttatntc  300
tgaacc                                         306

<210> 651
<211> 769
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1) ... (769)
<223> n = A,T,C or G

<400> 651
cattgtgttggcagggtca tttctaaggc atgggctgga agcttttatt taaaacttta      60
catgtcttag aagcactctg gttgttgcta ggcagacaat tttacatctc ttgctatacc    120
agttgcatga agttcatcat gcatattggc tgtggaaaac cttaacagca tcatgtcata  180

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aggtttcagt aaggtttaaa taaaatcatg tattaagcac ttagtatagt gcacccaaaa
 tgtagcttc aaaacaatga caacctaact aatgtgaaa gaagcttg tttgtaaatt
 atgttttatt gaaagatgtc atcaaaccct gttatttcta atcccttaaa gtctctcaat
 gtatccccc ttgccatata caatgacagg accttagttt aagccagtgg ttctctcaac
 ttctaatcca gagatacctg ggtgtccccca agacctttc agagcatcct tgatgtcaaa
 accattttca taataatatt aaaatattat ttgctcattt tactcttatt ctctccaaa
 tattcagcga gtttccaga agctatataa catgtggtaa catcttatca ctctgacgat
 taatagaata tgnngntttg gattcttngn tttaaaattt tctcaacttgg gggttctaat
 atggnnacga ttaatagata tggncat gaccagangg ctttaaagca ntcaataatt
 tttaagagac taagnactat cctttaaaga tngngaactc catcttaat

<210> 652
 <211> 267
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(267)
 <223> n = A,T,C or G

<400> 652
 nnangccctt taaccattgn ggcctccacg cnntggcggc cgctctacaa ctagnnggatc
 cgcnaactcta gnanaangat tggcttntt gggntgggccc ggnccggctg gggcgtaag
 cggggctggg cgcgccgn ggttgnacna ggccggcccg cccncacacn cccggagcac
 cctcnttgcn gcncntcccc gctcaccccg cgcgccgn tccgctttt ccncacccan
 agcnctnttt atctntgtct cctccgg

<210> 653
 <211> 501
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(501)
 <223> n = A,T,C or G

<400> 653
 cccnttnacc cattgctgga ctccaccgcg gtggcggccg ctctanaact agtggatcc
 ttncnatgag atgngcgang gaggacnnat ttgctatnct ggatgggct gantcnnnta
 gctnctctag cancagatgg gttatcgagg aagatgactc caangggcta nantcctatg
 cncatctaa aanncanctg ctgtnttcag agtacgcgac acatcatcnc tnatgcattt
 ntgancaaga cgggcangtg cttatcctca gcgangatgc ccttaaccan gagctcgaat
 ggacntatca ccntanaggt acanntnccg caccacacac cngcttgcnn cctgacgctg
 gactggatcn cttaggccac caatnccccg tttncacat ncctggacn ctananaaac
 tcganggggg gcccggtanc caattcgccc taataactgag cttgtntacg nacgctnact
 ngngntccta ttanaacggtt g

<210> 654
 <211> 710

<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(710)
<223> n = A,T,C or G

<400> 654

gcgnctttan cncatgctgg gctccacgcg gtggcggccg ctctacacta gtggatccca	60
acactgagtc caccacagna aaactcanca ccagcagac cccacaactg cagaatccag	120
gctgcaattc acagactaat cntctagacc cacctcagta ccagatggta ccacacagct	180
caaggntta ggtttgcgtg gtanactcaa tctctatctt tcaccactgc cagcctgact	240
ttagagatcc tgngctctgg acagtcctca gtggcaggca actctcagga gcctcaggnt	300
tttggcacat cccagnacca gccagctgcc acaggccctg accttntanc aacactgccc	360
atgttattcca gacttctanc ataccacagt gcatgctga ttgcatctat agangctcag	420
gtgcncctca aanctgtgcc tgctgcagna ngccccacgt ctctggcatg ccccaatgcc	480
atgngtggnna acanttgact tctgggcatg ntgaaattcc ctaccactga ncctgaccat	540
aggnggganc ccattttttt cgaggggggg gcccggcccc caattccncc ntatangag	600
ncgtanttac ggcgnctta ctngccngt ngttaacaa cgtcnntgan ctggggaaaaa	660
ccccctggnnng cnacccaa at taaacngcnt tgcannacat cccctttcg	710

<210> 655

<211> 202
<212> DNA
<213> Homo sapien

<220>

<221> misc_feature
<222> (1)...(202)
<223> n = A,T,C or G

<400> 655

cccccttncc ctttcanccc ccccgtttg gcngccgcn acacctactn catccaccca	60
cantcgacca cccgagcttt tttccgatcc cancatcnat gcngattttn tctntgcntg	120
ctgngcctgc acctttgnta ggtcaagcct gcccacatctt cgacaacttc ctcatcacca	180
acgatgaggc atactctgac ga	202

<210> 656

<211> 308
<212> DNA
<213> Homo sapien

<220>

<221> misc_feature
<222> (1)...(308)
<223> n = A,T,C or G

<400> 656

gctgntgaaa gaccacacccg aaaaactctn ctttccgact tccacatgat gatcngcatg	60
tggtggtag agacttatca tgacgacatc gttccnacc atcgcancn ctgccccagc	120

ccattcatgg	aggcctgggn	anttctgtga	ntgacntnga	cnctanacnc	tnccactgtn	180
tgctatccag	acttgnttng	aatatnttat	tggcnaaana	canttnccga	atgctgtgnt	240
tgnncattga	angatctgat	cactatgaga	gggtgaggac	nncctgctng	ctggcantnt	300
ntaaccn						308
<210>	657					
<211>	696					
<212>	DNA					
<213>	Homo sapien					
<220>						
<221>	misc_feature					
<222>	(1) ... (696)					
<223>	n = A,T,C or G					
<400>	657					
accnnttcca	caatnctgnn	ctccccgcgg	tggccggccgc	gtcgaccagc	aacctcagct	60
gtgggtcttg	ttacagtaat	gagttactgt	aaggaaaagtg	tgacatttcg	agcaatttga	120
tttgtttaaa	aactagagca	gtttcaggggt	tttccttgcata	aatctgtctt	atgtgtcttc	180
aatgttcttt	cttgaggagt	agagaaaagga	attgttagga	atgatgcata	aaccatggct	240
tatTTTATCT	cgctgccacc	cataatcaga	gcagattctt	gggactatga	ccctcatggaa	300
gacatgacaa	ttgtgtgtgt	ggtgggtggg	agaaaaagagc	tggaaatttt	taggtcttag	360
agggtccaa	caggactatt	ttatggagct	ctgctcacca	actttaagtg	agcaccagg	420
gtgngaaagc	gaatcttgggg	ntcaaaaanaa	caatggnaag	gggtaagttg	gtatnctgaa	480
ctggccactt	cggactctta	ttaactggg	tatttcant	taaggaggcn	ngggtgtct	540
tggcttgcna	aggaaagcct	gtgcaatgga	atgactttaa	aaccccccatt	taaaaaaaaaa	600
angntataaa	tcttgggtct	taanaanga	gcctgggttc	tnttanccca	ttttcccccc	660
gggaaggnaa	atnttcttag	gnaanggaag	ggaagg			696
<210>	658					
<211>	698					
<212>	DNA					
<213>	Homo sapien					
<220>						
<221>	misc_feature					
<222>	(1) ... (698)					
<223>	n = A,T,C or G					
<400>	658					
ctggactccc	cgcgggtggcg	gccgctctag	aactagtgg	tccgtgttgg	ctcaattctc	60
aaggctgttg	ctgtgcggcc	tgttccccac	acgtgctgt	cagctcaggc	aagcaccgag	120
cttgcgttgt	ttcatgtca	gcgtggaggc	ccctcctcca	ggtcgctgt	ctgtgggtt	180
cccatcacact	caggctccta	ggaggagtcc	atttagaaag	ccagggtttt	tctcagagtc	240
ttagttccct	gtgctgtcat	ccatccaca	cgacttggc	cctgctcggg	gcaacacagc	300
aagagaaaag	acaggaaaaa	taagagagg	accttgcaca	cacacgctct	ggaccacaga	360
gccctgtgcc	cagctccct	gtcaatacag	gtggaatctc	gtcaggatc	gcaggggtct	420
gtgatgccac	caaagagcag	gccgggacag	ggttaggaga	gaaaggagag	ggaagtgggg	480
gtttctccct	cgcactctta	tttgcagagg	gaaaggccgg	tttgtattgg	ggttgcgt	540
cttgcaccc	acngcacagt	tgtgagacac	ccccatctn	agatcaaagc	cccacataca	600
gcttggggaa	aaacaaaacn	aaacaaaaca	aaaacagtaa	acctccatgc	canttgttgg	660

gnaagtttn aatttncttc cccnacccan ctgcttc 698

<210> 659
<211> 750
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(750)
<223> n = A,T,C or G

<400> 659 60
ncaanctggn ctccaccgcgt tggcggccg ctctagacta gtggatcctc ctcatggcc 120
tggatatctc tgaacatatg atgaacattt cttataaaa attatttta ngaaaattgt 180
gaggcctaag aatgntattt tcttttagtg atggctttg tttgctctg taaggnactt 240
gtgggcactc gtaagcttgg atctcttaa tctaatacca gnnttgagat tttcttggcc 300
ccatagatga attaaaactg gcgtacttct tgtttacaag anggataagt ctccttagggt 360
aagtcttttgggtcccaag tcaaaaaagat gagggattta ccagttctct aaccttggta 420
gccccagact ccaaactttgccttctagtc ccaagaggct atcaaaaaagc aaaggccatc 480
ttccaccccttcccttccanaa cagcacacat tccagacagt acttggaaagc aggaacctcc 540
ttatccctta aaaaccttgggaancatct tccctcttctt gcttctacta tgcttggccc 600
acctancatt cnctttttc tggaaaccgg aaaaanccttngacttnngt tggctacatt 660
cagttggcc ccctacaatn tggttccat ctgccctaann gaaattttaa agggcacttt 720
tttntggcc cctgactttc nnnttttagg gctttcccccc angcttgcc cctttggta 750
aaggggttat ttcccttccc ctttggaaag

<210> 660
<211> 849
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(849)
<223> n = A,T,C or G

<400> 660 60
tcggatccac tagtccagtg tggtggaaatt cgccggcccg gtcgacgggc agtagtggta 120
tgcntntcta aatgttataa ttatccaga attactctgc cagaaagtta tgatcataca 180
tagaaagagtt ttagctaac tttgaaagta gtggaaagtg gtttcatgt attgtttggg 240
ttaatttaat ttgtattata ttgggtttt agttcaggtt attttttgt tgaaaacttc 300
aatgacaat ttcttcatgg ttactaaaga tcactcatgt ggagtagttt cagattttt 360
tctgaataca ttagtattttt ttagagatgtt aaagatgtga aattactaag agagaaaaccc 420
atgtgatttg ttagtggat caaaagtcgg tagctccctt gatcctaagt gccactgata 480
gttaaataga tactgaagct atggcaggc tggattgata agaaaaaaagg agacagagaa 540
atgggaaatt gggaaagaac tggcaataa gggaaaaggag agagcaacag aacagaatta 600
gtaccacagt gccaaggatgc cacctcaggat acttccatct cccatcttgc gagaattca 660
gtaacagttt gcaaatggtc aacacaatca tttagtgc tggattgata tttcaatac 720
tttctgggaa tttcttggct ggnttcaaaa gatgatgctg atagtttat tgccctgaa 780
ggtattctga agnttancat aatttattgg tcaqtaaaat atttgaataa aqgnqqanqa

aggaaaatct ggcnttttat tttggatnt cngcngggg aangaggata taattnacc	840
cggccttgg	849
<210> 661	
<211> 653	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1)...(653)	
<223> n = A,T,C or G	
<400> 661	
aacttaagct tggtaccgag ctggatccc tagtccagtg tggtggatt cgccggcccg	60
tgcacccca ttgcgttctt gtcctttttt ttcattttt ctcatgttctt attcacttta	120
ggtttctaag ataaatatta taaaataatt tttacttata aattattcac tgataccctg	180
tcttaacat gtgaaatgaa ttcaaaaagga atcttaatga gaaataatat actcatgtg	240
tttaatagat ttgatttcga aataataagc cctctgaagt cctaagttaa aaataaagca	300
acttggttga taattttca tcaagaatgt atctgagtct ctgagtaatt attagtagga	360
atattccatt atcacaatta cacagtataa gctatttagt ctaactttac caaaaaaggg	420
agctacttca acactgtgtg agactttaa tgggttgca ttgggtatgc actattagca	480
agataaaccta ttttacagca gtgtttnta accttccca tttatggaa aggtagctaa	540
gatatagttag ttaatntaan gggctgatgc atttatatta catgtagana atgggagata	600
cnaaaggag nggggggana ntnttgnat tcnnaagctt cttgncaat taa	653
<210> 662	
<211> 646	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1)...(646)	
<223> n = A,T,C or G	
<400> 662	
aaacttaagc ttggtaacccg agctcgatc cctagtccag tgggtggaa ttgcggcccg	60
cgtcgaccca gggacaggca gccagngctg gggtcaccag ggtccctct tggccctcc	120
aanagcaaca gtactggcaa cagctggat ttgctgagca cagactctgc agcaggctcg	180
gtttagctct ctgtgcctgt tccttcatac catctcacg cccatccatg agatgggtcc	240
agctgtttc agatgagaaa atggcacagg aagctggtaa gtgacagtca gaaatgaatg	300
ctggcagctt antccttggc cccaccgcag tgcaggacct tgctcaacag ggatcaccct	360
tgtccgccac ctgttcatga ggcacccag ggtttgtgtg gtcatttgc tccttcatc	420
tgcttgccct caaccagctg ggtcatttagg gctggggAAC ccagacccca cacagtccct	480
ctcccagang ccagacacan nctncgccac agnaaggact tcagccccg aancaaatgt	540
ncctggcggt anaaactgna gggncccaa tccctgggg ggtactgctt tgcaactggng	600
gaattcaccc ctcattgnna acctttccct nttnncaccc ctaaac	646
<210> 663	
<211> 650	

<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(650)
<223> n = A,T,C or G

<400> 663
aacttaagct tggtaacccga gtcggatcc ctagtccagt gtgggtggaaat tcgcggccgc 60
gtcgacgtcg acgcggcng ccgtttcgac gcagggtgata catattatta tataactacat 120
nggtttctta gaattaaaaaa attaatgtgt agtcccagcc ctagatgtaa gttacatata 180
tcaactctat ccaattttgt cagccataaa acttacctt ttcacatact tctaactctta 240
acaatgttag aatatgttagat cattgcaatt ataccacaa ggcagatggc tacatgcaga 300
atggatagca gaatctagct acttacgcta gccacatggt agacgtttt tcctttgttt 360
ttgcaaaaatt gcaatataag ttgcataatcg tttagtgaa aagatgtaaa gaacccatag 420
aagccagtga tgaaggacat ttatatttc acctttacaa angaccttaa aattgcctat 480
gtggagcaga aactggagga gggcnaancc atcngtaaaa aaaattttgn tnctatttgg 540
atttgggcac cattattacc tccccaggtt ccttttgnt ttaaccttcc ttttaaaaaaa 600
aataattcnt aatttttggg caaaaaaaaaa caagttttt atttaaattt 650

<210> 664
<211> 678
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(678)
<223> n = A,T,C or G

<400> 664
taaaaaatcta gactacacta ggaaattatt ttantatcg aagaatatca ggggtgttagt 60
actcatcana gctaaatgag agcgctttaa aaatgttagt ttgtcttccg ccatttctac 120
agaaaagctgc aatttcaggt tttcaaccta ataggtgata tttaaagaaaa aaaaaaaagca 180
atcgcaaata gccccactgc ttttacaaat catttttct cttcttaggtt tagcctgtca 240
ggtggcttaa tgtaattttt gacatctcta ggaattttaa tagaaccaga aatgggtgcc 300
agagatatgc ctgcactaat cttaagtggg gatttatgta tttctcaagc aagtgattaa 360
agcaaaaacta ggcacgattt aaatcaanat cttttaggca agaaagtcat gatgagtttt 420
anaatttattt taggactctg tggcttcctc ttcatagaaaa tagaaaaaaaaa aaattgtata 480
aaaaccacaa aaggtcctga atagcccaa gcaacactga acaaaangaa caaagcagga 540
agcaacacac taccggaaatt caattatact accaagggtgt antaacccaa acagcattct 600
attgggcata aaatagacca aagaccagtg ggaacacagaa taaagaancc caaaataaaat 660
cctatattta cngccnc 678

<210> 665
<211> 694
<212> DNA
<213> Homo sapien

<220>

<221> misc_feature
<222> (1) ... (694)
<223> n = A,T,C or G

<400> 665

cttttcaaat	cattttnct	cttctaggta	tancctgtca	ggtggcctaa	tgtaattttt	60
gacatctcta	ngaattttaa	tagaaccaga	aatgggtgcc	agagatatgc	ctgcactaat	120
cttaagtggg	gatttatgt	tttctcaagc	aagtgattaa	agcaaaaacta	ggcacgattg	180
aaatcaagat	cttttaggca	anaaaagtcat	gatgagttt	agaattattt	taggactctg	240
tggcttctc	ttcatagaaa	tagaaaaaaaaa	aattgtataa	aaccacaaaa	ggtcctgaat	300
agccaaagca	acactganca	aaaagaacan	agcagggaaag	caacacacta	ccngaattca	360
aattatacta	ccagggtgta	gtaaccaaaa	cagcattcta	ttggcataaaa	atagacacca	420
agaccaatgg	ancagaataa	agaaccccac	aaataaatcc	atatatntac	cgccanctga	480
ttatcaataa	cnaacaccaa	gaacatataat	taagggacnt	nctattcaat	aantagtgt	540
ggnaaaaact	gggaaatcca	tatgcagaaa	naatgaaaact	agacccctat	ccctcaccat	600
acgcaaann	caacttcgga	atgggattac	aaaacttaag	acattccaac	ccaagaaaact	660
atnaaanct	ctattaagaa	aacagatcnc	nccc			694

<210> 666
<211> 705
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1) ... (705)
<223> n = A,T,C or G

<400> 666

tttaaaaatt	tagatacact	angaaaatta	tttttagtatac	agaagaatat	caggggggtgt	60
agtactcatc	agagctaaat	gagagcgctt	aaaaaatgtt	agtttgcattt	ccgcccattc	120
tacagaaagc	tgcaatttca	ggtttcaac	ctaatacggt	atatttaaga	aaaaaaaaaa	180
gcaatcgcaa	atagccccac	tgctttaca	aatcattttt	tctcttctag	gtatagcctg	240
tcaggtggcc	taatgtattt	tttgacatct	ctaggaattt	taatagaacc	agaaatgggt	300
gccagagata	tgcctgcact	aatcttaagt	ggggattttat	gtatttctca	agcaagtgtat	360
taaagcaaaa	ctaggcacga	ttgaaatcaa	gatcttttag	gcaagaaaat	catgtatgagt	420
tttanaatta	ttttaggact	ctgtggctt	ctcttcata	aaatagaaaa	aaaaattgt	480
taaaaaccaca	aaaggtcctg	aatagccaa	gcaacactga	acaaaaagaa	caaagcagga	540
agcaacacac	taccagaatt	caaattatac	taccaaggt	tagtaaccaa	aacagcattc	600
tattgggcnt	aaaatagacc	naagaccaat	ggaacagaat	aaagaaccca	aaataaatcc	660
atattttac	agccagctna	ttatcaataa	aaacnccaag	aacnt		705

<210> 667
<211> 817
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1) ... (817)
<223> n = A,T,C or G

<400> 667

nnangacttt	tgtggtnnta	tacaattntt	ttttctat	ttt	ctatgaagag	aaagccacag	60
agtccctaaaa	taattctaaa	actcatcatg	actt	cttgc	ctaaaagatc	ttgatttcaa	120
tcgtgcctag	tttgcttta	atcacttgc	tgagaaatac	ataaaatcccc	acttaagatt	180	
agtgcaggca	tatctctggc	accatttct	ggttctatta	aaattcctag	agatgtcaaa	240	
aattacatta	ggccacctga	caggctatac	ctagaagaga	aaaaatgatt	tgaaaagca	300	
gtggggctat	ttgcgattgc	ttttttttt	tctaaaatat	cacctattag	gttggaaacc	360	
tgaaaattgca	gctttctgt	gaaatggcg	aagacaaact	aacatttttta	aagcgcttc	420	
atttagctct	gatgagtact	acacccctga	tattcttctg	atactaaaat	aatttccta	480	
gtgttagtcta	aacttttttta	aaaagacatg	taatcccg	agtttgc	taacaaacgag	540	
tgcatctagg	aggtatcgca	agccgttct	ggattaaattt	cccagctagc	ttgcttgctt	600	
agcagggggcg	gnnaanaaag	acatctgcag	cctagggaaag	aaaaccttc	gcattgttct	660	
tacgttta	cgttatttttta	ttccctanaa	caaggcngaa	ttgggactcg	aatggttcag	720	
ttgggggtggg	ggatcccctg	gtncataaaaa	ngtcanaaag	anggtacagg	cggaacncca	780	
agggtcg	tgcatttana	ctcggattt	ttgtgcc			817	

<210> 668

<211> 826

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(826)

<223> n = A,T,C or G

<400> 668

cgggggggnnt	tacgtctctc	tggacgctt	tattgtacca	gggcgatccc	agcccaactg	60
taccattcga	gtccctactc	ctgccttgc	ctagggaaat	aaaataacgt	aaacacgtaa	120
gaacaatgcg	aaagcg	tttccctagg	ctgcagattt	tcttcttac	cgcccctgct	180
tagctagcta	gctagctggg	aatttaatcc	agaaacggct	tgcgataacct	cctagatgca	240
ctcgtttga	gttacaaact	ccgcggat	catgtctttt	taaaaaagtt	tagactacac	300
tagggaaat	tat	tttagta	tcagaagaat	atcaggggt	gtagtagtca	360
atgagagcgc	ttt	aaaaatg	ttagttgtc	ttccgcatt	tctacagaaaa	420
cagg	tttca	ncctaata	agg	tgatntaa	gaaaaaaaaa	480
gcttttacaa	atcattttc	tcttcttaggt	atagcctgtc	agg	ggcccta	540
gacatctcta	ggaattttaa	tagaccagaa	atgggtgca	gagatatg	cc	600
ttaagtgggg	atttatgtat	ttctcaanca	agtgattaaa	gcaaaactag	gcacgaatga	660
aatcaagatc	tttaggccag	aaatcatgaa	nan	tttana	attattttan	720
cttctttct	taaaatngaa	aaaaaaatg	tttaaacc	naagg	tctga	780
ncctgaacn	anagaacaan	gccggagcac	ccc	ctccaa	atcccc	826

<210> 669

<211> 547

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(547)

<223> n = A,T,C or G

<400> 669

cattgtgttggaaaaat gatttgtata agcagtgggg ctatttgcga ttgcgttttt	60
tttttcttaa atatcaccta ttaggttcaa aacctgaaat tgca gcttc tgtagaaatg	120
gcggaagaca aactaacatt tttaaagcgc tctcatttag ctctgatgag tactacaccc	180
ctnatattct tctgatacta aaataattt cctagtgtag tctaaactt tttaaaaaga	240
catgtaatcc gcggagttag taactcaaaa cgagtgcate tnngaagttat cgca gccgtt	300
nctggatnaa attcccagct tgctngctg ctnagccggg gggcggttcaa aaaaacatct	360
gcagcccnngg ggnaaaaacc ttgcattgt tcttacgtgt ttacgttatt ttat tccct	420
nnagcaaggc nggganttgg ggactcgaaa tgg tacagttt gggctgggaa tcgccc ttgt	480
tacataaaaag ncgtccagaa gagggacggt tacaggcngg ganctccaaa ggtcagtccc	540
tgccatt	547

<210> 670

<211> 232

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1) ... (232)

<223> n = A,T,C or G

<400> 670

cgaactattt agactaccta ggaaaattat ttttagtatca gaagaatatac aggggtgttag	60
tactcatcag agctaaatga gagcgctta aaaatgttag tttgtcttcc gccatttcta	120
cagaaagctg caatttcagg ttttcaacct aataggtat atttaaaaaa aaaaaaaaaagc	180
aatcgcaaat agccccactg cttttacaaa tcatttttc cccaacacaa tg	232

<210> 671

<211> 214

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1) ... (214)

<223> n = A,T,C or G

<400> 671

ctccccttcc ntccttcgct actncncatt ttcnnaaatt ntnttcgcnt atngggaaaa	60
acacccacat ntntcanctc gcacagaaca ngnnggggtg tgtaaaaatga aggcttccn	120
cnctttctct tattnaanaa cactnaanaa gggangggct aaaacccgcg ngatntctac	180
nctatcgccg gcgctttgg ngtggctag aaga	214

<210> 672

<211> 328

<212> DNA

<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(328)
<223> n = A,T,C or G

<400> 672
ngancagcg ngttaaacg ggcctctaga ctcgaggaga cnccgttgg atggggatc 60
acanntcgnt actactatac aggacagagt atcggganct ctggntgtt ggngcctgcc 120
aaccactgtc nctgttaact gcgttatctga agggactcgg actggcttca gaagaactac 180
cggtcgaa gnaccatgga tgattcncnc tagtgaaaa aaaactcagg cacatgtatt 240
gccactgatg actagcgcca gactnctctc ggctctntaa cgagcccaca tgnncngtgc 300
ncnccgtgc tgnctccaga agaggttc 328

<210> 673
<211> 223
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(223)
<223> n = A,T,C or G

<400> 673
gggggcaaa ctggctagcg tttaaactta agcttgtac cgagctcgg tccccnnagac 60
attgtcatg aaaatgcaaa ttgagtgtgg tctatantgc catcntcacc tnctgncngc 120
tcaaaaacaac ngcttctgc tgcaatgggt agggctcctn acncacggc gcnnacggag 180
gccnncttat cctcnctcggt nnggatccct ngaagcatnt tct 223

<210> 674
<211> 256
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(256)
<223> n = A,T,C or G

<400> 674
gnngggtcnt ngatgagcgc gcgtaatacn atcactntcn ggcgngntgg gtacggggcc 60
ccccctcnaa cgccggccccc ttttttntt ttttttcatn acatgataan ntcttnttc 120
taaacagacc acaccactan agttcctttn cttingtacg gaattgagtt aaagtagagn 180
atacaatgca gggctcnnc tctatttac attccaggnt ggttcngnat ggatcgccc 240
tgcctctccg atgggt 256

<210> 675
<211> 439
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(439)
<223> n = A,T,C or G

<400> 675

nnactagtcc	agtgtggtgg	aattccattg	tgtgggctt	gtatgggttt	ttttgtctag	60
ttntttggga	aatgttngtg	ttactatntt	ttggatatna	tatatgatat	gtatggccct	120
tctatgggct	cctcanacng	aactcaacca	ttttccacaa	aaccnattcc	tcctttccct	180
tcatgactga	gtgggtttgg	tactatccng	gaaactggga	cattgtcctt	cacatctntc	240
ccttanctgc	ctngtccnat	tgatgtctt	gagctntgan	atgtcttgt	taactntctc	300
ctncntctgt	actgccggca	naattaagca	ccatntgtca	aaaaaagtat	tgcgttacct	360
tcacgnatct	gttngtncc	atncttgctg	cttctccngn	ggaaaatagg	ctnttctggc	420
aaccgaacng	aanaaaatac					439

<210> 676
<211> 587
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(587)
<223> n = A,T,C or G

<400> 676

nggnggcctn	attaagcgcg	cgtataatacna	ctcactntgg	ggcgaattgg	gtaccggnc	60
cccctcaagt	tnatntgccn	aacctctctt	ttggaataac	aaaagggtta	acacatatgt	120
cctcataggg	acgcgccttc	acacnttcct	gacngcttca	tanacntcat	tnctatttct	180
cctcagnaca	agttttaggcn	gaaggtgagg	canacnttat	aatttccatt	tcacaaatnc	240
ggaaaagttag	gctcaaaggg	ntaaaaaaaaat	aacctgatac	aantcataga	gccggtnct	300
ggaanaagca	ggagcaaaat	ccaggcatcc	tgatccaagc	tnggtccact	gccttccact	360
ctggagaggc	ttcatctccg	acaaaggaag	ggacntgagt	ggctgganaa	tctcatggga	420
taaagacctc	agnatttcat	gctcctggaa	atcccatggg	ttgaacaaca	ggtnnttggc	480
ccgtggttct	ntccctttgn	ccatcttttta	accttgggtt	aaatgatggc	ntctntnagc	540
nttttttttn	aaagagatng	aaattgaatg	attatngct	cattggg		587

<210> 677
<211> 444
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(444)
<223> n = A,T,C or G

<400> 677

gtggggcain	attaagcgcg	cgtataatacga	ctcactatag	gggcgaantg	ggtaccgggc	60
ccccctcgaa	gcggccgccc	ttttttttt	tttttactgt	ccaaactntc	tatngatnta	120
gttgaactgt	ncaacgattt	catgaaatc	tatacacacana	gccttcaggt	ccagagagta	180

aaacaaaattt aaatttnttc accanattgn agcagncana agcatccnat natatccgac	240
tacaatgaat natatgctna nggtanctna tttacccact ntgggtctt tanggtctgt	300
cacaaaactat ttccgtaaac atcnntttaa anttnggtga atggacctaa tnccagataa	360
ntctatttna tntaccctag catncctgtg gctnacttn cgggctgtgt tggcntactt	420
ttaggagaaa attggataaa atnn	444
<210> 678	
<211> 670	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1)...(670)	
<223> n = A,T,C or G	
<400> 678	
actagtccag tgtggtgaa ttccatttg tgggagcag tttaaaaaaa aaaaagacna	60
aatatacnac tcttgatnaa acataaaagt acagtggtct atgaggaana gaaaaggta	120
ctnaggatgc aaaantacct accacatggg aaccgttgt ccacactcat tccnnanaaa	180
accgagtcct ctcantnca cacgtgtacg tttcagttgg gaagtgcttg ccattactcc	240
naaggctaga accttcacgt cctgaagggtt ctggaagggtt tttcagattt cttaaganac	300
gcngcccttc catattcntc tccactaccc ngggaacgg aacaaatgga gctgcacng	360
ggaagcgtcc cttccntcc gaacgccttc tttcaaaccct gcctgccttc cnngcgaatg	420
gaccggaagg ttnctngct tcctttcanc ccnaattact tcctgngttt aaaattggcc	480
tgttggtttt caaatgcngg aatttgtta ctttcntcat gtccctgtgtt gnncnaaccg	540
gtcncttgt tgcctccctt tngaaagggtt ttcatcaggc cccgcccctt ctctntaan	600
ngtcctaattc cggnncnggac cactcgggaa aaattttttc tttcgaaaa gccgccccnt	660
ccgtccggct	670
<210> 679	
<211> 449	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1)...(449)	
<223> n = A,T,C or G	
<400> 679	
actagtccag tgtggtgaa ttccatttg tgggagtag gtctactaca ncctacttcc	60
cctatcatan aagancttan caacnttcat gatccccccc tcntannct tttcctcanc	120
tgcntcttag tcctgtttgt cctnttccta acantcntaa ganagatnac taatnctact	180
atctctnacc tccggaanc tacaanacgtc tggaactatt cngaccccat gcancncat	240
nctccatcgt cctcccagcc cctnccttc cttaacntta ctnaacgaag gtcgacgatc	300
cctccntac ctccccnncc attgggnccc aangnactg gacctcacga ntacaccnac	360
tacggggnga ctaagnctgn aactccttac atatntcccc gttaccccn gaaacncagcg	420
aacngcnaca ccttggacnt caagaanta	449
<210> 680	

<211> 670
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(670)
<223> n = A,T,C or G

<400> 680

tttcngtgtg	gtggaattcg	cggccgcgtc	gacgagaaga	nggaggagga	naaggagaag	60
gagaagaagg	agaanaagga	ggagaaggag	aagaaggaga	agaaatcatc	atcatcatca	120
tccactgtct	ngcaactatt	taagttgcn	antcccttga	aaacaggtag	ttttgtttca	180
atgtttggga	ccactnctga	cnatgannag	aanaccaata	aatgcttgat	naatgaaaaaa	240
nccactttt	acctgttaga	accctgaggc	taagagaant	gatgtgactc	gacttagtta	300
ccacaaaacta	tgatccttagc	atnaattggg	gcatctcaac	acctcaactc	cctgtgcaag	360
aacagatttt	caatgtctac	tgatgatttt	aatggatta	nttcctctct	ttacttctta	420
agggcatgaa	gnnttatgaa	acaaaaactat	ncagttccag	acgcttaacc	cacatagtgt	480
taatagtcac	cttcaacaca	cnaactaaacc	ccccaaaaan	gnnttttacg	gnntttcgac	540
agttttcttt	tcttttgac	ttgnttaaca	cccnngacaa	ctttgtnctn	tttccntgaa	600
tcacanctt	cnaanancca	atggtnccgt	ttttctcnt	tcngggccct	tccctnttn	660
aaaaccanat						670

<210> 681
<211> 494
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(494)
<223> n = A,T,C or G

<400> 681

tcatggtgtc	cacagtctga	tgtgagcgca	ttaaatttaa	ggatctccgc	ccttctcctt	60
aaaactcagg	acttggcaat	ganccttaga	agcgcgcgc	ccctccccc	ccanatccaa	120
gccccggacc	gctgcgnctc	cagctgcgcc	tagtggaaacc	gccgaattcg	aattcacact	180
cggngggccg	gcgaagggtgt	gcgcgcgcgc	gggagcgccg	gggcnagccc	gagggactgc	240
aagccaanaa	nggaggcatg	gttggcgggg	ggcgcgcgtct	gatccagggaa	ggagcggagg	300
cgccgatcac	acactctna	gacgcccgtc	ccgcgcctgg	ccagcgcgca	gnctgcagga	360
cgegcggagc	aggaactcgc	tggagtttgc	caagccccan	gnctctggaa	agtntgttagc	420
tccccttcgg	ancgnctt	ctggcccttt	gggacgggtg	tgtcattggg	cgggggtctg	480
tataaggggg	ggac					494

<210> 682
<211> 263
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature

<222> (1) ... (263)

<223> n = A,T,C or G

<400> 682

tgatcattca	agcgntgngc	gnataaacat	tgctnagccc	aaccttcat	agggtcggttc	60
ctttggaaat	nggatgtcta	ttgaatggca	gggatagggg	cactcggcat	tcgcctctgg	120
tacagttttg	catatatatc	ctcatcgca	gcgagcgtag	ggganctta	agtttggga	180
aatgccnccg	catgnccctn	ccggagctta	aaccccaac	aatncccatt	tnaaaaaaag	240
nttntttant	aaaaaaaaa	aac				263

<210> 683

<211> 255

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1) ... (255)

<223> n = A,T,C or G

<400> 683

cttggccggc	atgcacagac	ntntttacgg	acacnctact	ccaagngagc	ctgnanctgt	60
ctacggtaaa	nctctaagg	tngncantgc	cacanatggc	atagtcccg	gggcggtnan	120
tctggantgc	tctctgcact	tgaacntaaa	ggcgcnttca	aganaggnc	aatngcctgc	180
ctcttgacaa	cnaacaanc	cacaccnacc	tangaccctn	tangcaagga	ctggattctg	240
naaatgcaat	acaca					255

<210> 684

<211> 922

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1) ... (922)

<223> n = A,T,C or G

<400> 684

acccttcatt	tcatgtgctt	ctatttcct	acatttta	catgactaag	ggattaatga	60
aatcacctct	tcataatcat	gaccataatt	tcatccaaca	agtactcaag	tttgggttta	120
gcactttatt	aatgcttacg	atttctct	ctctccctct	ttctctttc	cttagtcctt	180
gcacaataag	gattttgaa	tgtataat	catcttaggt	aagcttcat	atggtttgg	240
catatgaagc	ttatgactgt	cataagccat	accaagcctg	tggagtatgg	catgattttc	300
attacataat	ccaataaaaa	tagacttatt	ttaaatccct	aactttgtag	tttaatttg	360
tatccacta	tcttgaatt	aacagctagt	acttatccat	cacagcagtc	tcctactgac	420
atgaagcaag	tttgtgaatg	cagtaganca	tgaatgaaag	catttaatgt	tanacaaaaa	480
tgggtgatac	ccaaggattc	tgaatttattt	gcatcaagga	atgggacatg	tacatttagtg	540
gcatcatttc	taccaatatg	tgacttgaat	tgtttttta	aaaaaaggan	aatgantttc	600
tcaatttgc	ttaaaaaattt	ttnaaaaaagt	tcaatggcat	gctgcttgc	ctggacttaa	660
tttattaaca	attnttaanc	cttccttaag	gacanaattt	tgggtttcag	gatcncccctg	720
agggtctta	tttttnatan	nattccaaac	ccaaaagggtg	gtttaaaatg	ggnggggttcc	780

ccccncnaaa attggaccc gctttttat attaaaaaaaaa nttnccntt gngtttgaaa 840
nctnaatacc aattaagggg gaattttacc tnccagtggg aaaaaaaaaac nctngccntt 900
aaaaaaaaattc ccnggagnca at 922

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<210> 685  
<211> 531  
<212> DNA  
<213> Homo sapien
```

```
<220>
<221> misc_feature
<222> (1)...(531)
<223> n = A,T,C or G
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<400> 685	tgaggctctg taaaactgtt cctctgctag gcatacttca tattctctat attaaactca tcttaattg gcatggaaga ttcatgttc caaatctcg atgaagatcc tatattggat gcaattaagc ctggcagcgc cctcaaaaga cagtcttgc actgctagcc acagccagga cacagtaaca gttccttcta gtgaccnag accataanaa atananaatct aaagaattct gactccaaag gcatttagccc attcctggta ttgccaattt tgatagaaaa aattgccaag ctcctggac atggaaatac actcagtgata ttgagaact ggagaactan tttccaaaaat agtatgaaga catganggtg atttagata tntgagttg gagaantga gggaaatcng attacacatg ttactacaa gagatgttna taagtaaaga aggctgtata tacaatctaa cagacnangt agataaatct taantcacaa ctgacntccc tttggggcg g	60 120 180 240 300 360 420 480 531
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<210> 686  
<211> 336  
<212> DNA  
<213> Homo sapien
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<220>
<221> misc_feature
<222> (1)...(336)
<223> n = A, T, C or G
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<400> 686
ggngnctna tgagcgcgtaatacgtatc atataggcg aattgggtac cggggcccccc
tcaagaacac tacaagcttat gtcctttct canagagccc tgaantttta acatattgaa
agctctnata ttgccaaana actccactta acttcaaaac acaccctcca cacacatcat
gatcaactna gatcttactg aaccagaatc cttaatggca tacttcagga acaggggtcc
anagaagcag ttctcaaant gcagctnaaa aagaaaactga aaaccctaatt catgcaanac
ctagggctta tttqagagca tttccagtgcagatt

```
<210> 687  
<211> 271  
<212> DNA  
<213> Homo sapien
```

```
<220>
<221> misc_feature
<222> (1)...(271)
```

<223> n = A,T,C or G

<400> 687

aatctgcact ggaaaatgct ctaaaataag ccctaggctc tgcatgaatt gggtttcag	60
tttctttta agctgcactt tgagaactgc ttctctggac ccctgttccct gaagtatgcc	120
attnaggatt ctgggtcagt aagatctcag ttaatcatga tgtgtgtgga ggggtgtgtt	180
tgaagtnag tggagttctt tggcaagatc agagcttca atatgttnaa acttcaggc	240
tctctgagaa gaggacatag cttgttagtgt t	271

<210> 688

<211> 740

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(740)

<223> n = A,T,C or G

<400> 688

tgatgaagcg cgcgtnntac nactcactat ngggcgaan tatgggtacc gggnccccct	60
cgaagcggcc gcccctttt tnttttttg tgagagttt aataaaatat ttgagtttaa	120
tttaaagttt gagtttaatt aaaatatatg gcatatccca agttggcctt tgcanaaaga	180
acacttctca ggaactgtt a gttgggttac caggaactca gaagggtcct gttattaaat	240
atatttggaa aatgcatgga ttctctgaan atcnctctgc atgtgagcaa cacttacatc	300
ncaaaccaaa attggcattt catacatnaa ccaatatttcc caaaacattt ctggttatgg	360
cccacccctt ttgtgtanta cttattgctg tttttggaa ccctgggaa attacttaaa	420
atattcagct ggaaattaca ggcgttaccc ttaaggganc aagaattaca gtgactccca	480
aaatttgcag tggatttac tatttaagaa cccaagaatt taaaagaaat tttgaaaagt	540
aaaaacngga aatnttaaat gacttctcaa attttgaaaaa ctcnngnnaaa catctccact	600
ttggtnccct tcctttaaaa attggctaaa aatntttnt tatnccacc ccattgaaan	660
tnccccccccc ctggaaacaat tggattcccc tatttcctaa aaaacggccn ccccccccg	720
ggngaacncc nacnntttgn	740

<210> 689

<211> 635

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(635)

<223> n = A,T,C or G

<400> 689

actagtccag tgggtggaa ttccattgtg ttgggattac atatactttt agcaattttt	60
aaagaagtgt acaaagttaa gatgtttcct gagctctcat atatctgana atgtcatttt	120
acatctccgt cttcacctt caaaacttct ttcaattttt tggctcttaa tagtaatcaa	180
cacttgcact ctggagtac tggattttt gctccttac agctacnccct gttatttcca	240
gctgaatatt tttagttatt tcccagggtt ccaaaaaaca gcaataagta ctacacaaag	300
gggggtggcc ataaccagaa atgtttggaa aataactggct catgtatgca atgccaatc	360

tggtttgcna ttgtantgtt gctcacatgc agagtgaatc ttcaaanaat ccatgcattt	420
tccaaatata ttaataaca gggAACCTC tganttcctg gntacaccaa ctaacagttc	480
ctgaaaaatg ttcttctgc aaaACCCaaC ttggggatat gccatatatt ttaattaaac	540
tcaaaacttta aattaaactn caattatttt attttaaact cctcaaaaaaaa aaaaaaaaaa	600
aggggggggcc cttccaangg ggggnccggt tcccc	635
<210> 690	
<211> 3923	
<212> DNA	
<213> Homo sapien	
<400> 690	
acagaagaaa tagcaagtgc cgagaagctg gcatcagaaaa aacagagggg agatttgtt	60
ggctgcagcc gagggagacc aggaagatct gcatggggg aaggacctga tgatacagag	120
gaattacaac acatatactt agtgtttcaa tgaacaccaa gataaataag tgaagagcta	180
gtccgctgtg agtctccctca gtgacacagg gctggatcac catcgacggc actttcttag	240
tactcagtgc agcaaagaaa gactacagac atctcaatgg caggggttag aaataagaaa	300
ggctgctgac tttaccatct gaggccacac atctgctgaa atggagataa ttaacatcac	360
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ccccttaaa tatccacaca cacaggaagc acaaaaggaa gcacagagat ccctggaga	480
aatggccggc cgccatctt ggtcatcgat gaggctcgcc ctgtgcctgg tcccgcttgc	540
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tcctgttgtg gatattatt tgaacgggat tacagattt aatgaagtc acaaagttag	660
cattaccaat gagagggaaa cagacgagaa aatcttgatg gcttcacaag acatgcaaca	720
aacaaaatgg aatactgtga tgacatgagg cagccaagct ggggaggaga taaccacggg	780
gcagagggtc aggattctgg ccctgctgcc taaactgtgc gttcataacc aaatcattt	840
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ttctcagcag aagccagaat ttgaattccc tcatactttt ggaatcattt accaggtttgc	2520
gagaggattc agacagctca ggtgcttc ctaatgtctc tgaacttctg tccctcttgc	2580
tgttcatgga tagtccaata aataatgtta tcttgaact gatgctcata ggagagaata	2640
taagaactct gagtgatatac aacattaggg attcaaagaa atattagatt taagctcaca	2700
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tcttggcata ctatataac ttgttattttt tgttacaact tttcttactc ttttatttacc	3600
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tacctaattgc atgtggact taaaacccatg atgtgggtt gataggtgc gcaaaaccact	3840
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<210> 691

<211> 882

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1) ... (882)

<223> n = A,T,C or G

<400> 691

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cctgcactcc agcctggatg acagaacacg atcatttctc taaagacaaa caaaaaacat	120
aaaataaaaac tagtataagg atagaagccc aggggttgcatt taagtctgcg gaaatcataa	180
accatagggtc agacttctca ttgtatggatg acttgtgggt tagaatacataa ttgttatata	240
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gtcaattcca gttctaaaat tccatcactg ngcactaagg caaattgaat tgaataaaatg	540
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gacgcantca tccagncatc tcctaccctg ncccatgnnc tatgtagana tgcgttctca	660
atcccttaac aaaccgattt tgccaaaggag cttanccttgg gggtaacttgg tcanggcaac	720

tggtctactt tnaagactca tcttcactta ctggcacca aatncctacc attgcatcaa	780
actggggttc ccatncaagg caaacccctgn gaaatcttta atcccgaaat tggcgcccaa	840
ttttnnnnnn ttccnnaaaa gaatcntccc ccccgagggg cc	882
<210> 692	
<211> 235	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1) ... (235)	
<223> n = A,T,C or G	
<400> 692	
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ttgatggtaa aagggttagct tactggnatg tccgnctgct ccanganata atacncagga	120
cttctcanag cacttaatat gttaatataa aactncgnga aaaaagatnt tcnatgaanc	180
nttcctctta ggaggtcagg ngagaatagt gttaatgnca ttaagganag aacga	235
<210> 693	
<211> 383	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1) ... (383)	
<223> n = A,T,C or G	
<400> 693	
nttatgttaa aatgtcata tatctttat tttctttaaa tcaaaataaa tatgactttg	60
agcatcccat cccatgcccc atcctatcag aatggtagga acatcaacac aaataattag	120
taatgcaccc catctacatt cccatgctct cttaacttct tcagcattgc ctaaaggcat	180
aatacacctt taattaatta attcagccctc ctaatgcaca ttaacaaagc ccctgctaga	240
ctctgtccat aatggnaaac ctgnatgatc cttgatattta acantttaag gaatgctcat	300
ggattggtnn cagacttaaa aaattgaggg ggctgaanaa aatctaangg anaaatcatg	360
gaagcatttg cacatattac ata	383
<210> 694	
<211> 204	
<212> DNA	
<213> Homo sapien	
<400> 694	
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actgtccctt attttttcc ctcccaggct cataactcga ggttaaactc tctttatac	120
aagaaccctg tctgatgaag catcattca gaattttaag tcaacttaca aatgtggat	180
tattcacatc tgagtacaaa ttta	204
<210> 695	

<211> 670
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(670)
<223> n = A,T,C or G

<400> 695

gcaccagccc	aggtgctgtt	tcttcacttg	agctccatga	ccctccctgt	gtggtgggtt	60
gaacgggtac	ctccaaaaga	tatgtccacc	tggaacctca	gaataagatc	ttatttggaa	120
tagtcttgt	agatgtcagt	aaggtaaaga	tttggagatg	agaccctcct	ggatttagggt	180
aggccctagg	tccactggca	ggtgtgctc	tcagggctcg	aaaggggaag	acagggccac	240
ccagaggagg	agacggaggc	agagacaggg	ccaccagag	gaggagacgg	aggcagagac	300
agggccaccc	agaggaggag	acggaggcag	agacaggggc	cacccanagg	aggagacgga	360
ggcagagaca	gggcaccca	gaggaggaga	cggagggcaga	gacagggcca	cccaaaggag	420
gagacggagg	cagaanacag	gcccccccaa	agaaganacc	ggaggcanaa	aacagggcca	480
cccanaggag	gagacggagg	canaaacagg	gccaccccaa	aggagggagac	ggaggcaaaa	540
cagggccacc	caaaaggagg	aagccggaag	gaaaaaacag	ggccccccca	aaggaggaag	600
ncggagggcn	aaaaanaggg	cccccccaa	agngagaaaa	ccnggnaggc	nanaaaaccn	660
ggggcccnnc						670

<210> 696
<211> 317
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(317)
<223> n = A,T,C or G

<400> 696

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gcccaactgtc	atcgtggata	catttcactt	ttttcacatg	actaaggagc	tctccggagt	180
gaagagttag	taaatatgtt	tattacgat	tcatttgcta	agaatcatca	agaacccaaa	240
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ctggatctgc	tggtgcc					317

<210> 697
<211> 246
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(246)
<223> n = A,T,C or G

<400> 697

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ggatcctcn	anagcggacg	cctactacta	ctaaattcgc	ggncgcgttgc	acttttttg	120
ttttttcc	tnacagagnt	nttttgtgc	ccttggttct	tatgctcana	ctcngcaaaa	180
aanatcaaaa	gntacnnatg	aaaaacntat	nccatctnca	naaaggaggt	gnagntatta	240
ctttct						246

<210> 698

<211> 3674

<212> DNA

<213> Homo sapien

<400> 698

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agccagtgaa	acatattcct	tcttctctcc	atcaggccaa	atcacggtgt	tgaccttggc	180
cacatcaatg	tcttagaact	tcttcacagc	ctgtttgatc	tggtgcttgt	tggcttaac	240
atccacaatg	aacacaagtg	tgttgttgc	ttctatcttc	ttcgtggta	ctcagtggtc	300
agcggaaact	tgatgatagc	gtagtggta	agcttgtatc	tcctgggagc	gctcttccaa	360
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<210> 699

<211> 2051

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(2051)

<223> n = A,T,C or G

<400> 699

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aaagaagcaa	aagtcttagg	aaaatgaagc	aagtgcctt	gccactctat	gtacagtaat	1980
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<210> 700

<211> 2841

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1) ... (2841)

<223> n = A,T,C or G

<400> 700

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<210> 701
<211> 3228
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1) ... (3228)
<223> n = A,T,C or G

<400> 701

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10

15

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Asp	Arg	Leu	Val
Gln	Arg	Phe	Gly
		Thr	Arg
		Ala	Val

20

25

30

Tyr	Leu	Ala	Ser
Val	Ala	Ala	Phe
Pro	Val	Ala	Ala
		Gly	Ala
		Thr	Cys

35

40

45

Leu Ser His Ser Val Ala Val Val Thr Ala Ser Ala Ala Leu Thr Gly
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 Phe Thr Phe Ser Ala Leu Gln Ile Leu Pro Tyr Thr Leu Ala Ser Leu
 65 70 75 80
 Tyr His Arg Glu Lys Gln Val Leu Ile Gly Gln Trp Val Glu Ser Gly
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 Ala Ala Gly Ile Thr Tyr Val Pro Pro Leu Leu Glu Val Gly Val
 35 40 45
 Glu Glu Lys Phe Met Thr Met Val Leu Gly Glu Ser Leu His Pro Pro
 50 55 60
 Ser Phe Leu Phe Gln Ile His Ala Thr Trp His Val Gly Gln Glu Tyr
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 85 90 95
 Ile Ala Gly Gln Glu Gly Asp Pro Gly Leu Arg Gly His Thr Lys Arg
 100 105 110
 Lys Lys Arg Ile Pro Arg Thr Tyr Pro Ser His Leu Trp Ile Pro Gly
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 Leu Trp Leu Ala Leu Leu

145 150

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Leu Tyr Leu Ser Gln Pro Leu Thr His Thr Thr Ser Leu Leu Ala Gly

20				25						30					
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Ile Gly Pro Val Leu Gly Leu Val Cys Val Pro Leu Leu Gly Ser Ala

35				40					45						
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Ser Asp His Trp Arg Gly Arg Tyr Gly Arg Arg Arg Pro Phe Ile Trp

50				55					60						
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Ala Leu Ser Leu Gly Ile Leu Leu Ser Leu Phe Leu Ile Pro Arg Ala

65				70				75				80			
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Gly Trp Leu Ala Gly Leu Leu Cys Pro Asp Pro Arg Pro Leu Glu Leu

85				90					95						
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Ala Leu Leu Ile Leu Gly Val Gly Leu Leu Asp Phe Cys Gly Gln Val

100				105					110						
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Cys Phe Thr Pro Leu Glu Ala Leu Leu Ser Asp Leu Phe Arg Asp Pro

115				120					125						
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Asp His Cys Arg Gln Ala Tyr Ser Val Tyr Ala Phe Met Ile Ser Leu

130				135				140							
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Gly Gly Cys Leu Gly Tyr Leu Leu Pro Ala Ile Asp Trp Asp Thr Ser

145				150				155				160			
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Ala Leu Ala Pro Tyr Leu Gly Thr Gln Glu Glu Cys Leu Phe Gly Leu

165				170					175						
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Leu Thr Leu Ile Phe Leu Thr Cys Val Ala Ala Thr Leu Leu Val Ala

180				185					190						
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Glu Glu Ala Ala Leu Gly Pro Thr Glu Pro Ala Glu Gly Leu Ser Ala

195				200				205							
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Pro Ser Leu Ser Pro His Cys Cys Pro Cys Arg Ala Arg Leu Ala Phe

210				215				220							
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Arg Asn Leu Gly Ala Leu Leu Pro Arg Leu His Gln Leu Cys Cys Arg
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Met Pro Arg Thr Leu Arg Arg Leu Phe Val Ala Glu Leu Cys Ser Trp
245 250 255

Met Ala Leu Met Thr Phe Thr Leu Phe Tyr Thr Asp Phe Val Gly Glu
 260 265 270

Gly Leu Tyr Gln Gln Gly Val Pro Arg Ala Glu Pro Gly Thr Glu Ala Arg
275 280 285

Arg His Tyr Asp Glu Gly Lys Ala Leu Ala Ala Ser Arg Gly Trp Cys
290 295 300

Gly Ser Arg Pro Pro Glu Thr Thr Leu Gly Ala Val Ser Gly Leu Val
305 310 315 320

Pro Leu His Pro Gly Pro Asp Phe Ser Val Arg Lys Val Gly Met Asp
325 330 335

Pro Ile Cys Ile His Gly Phe Ser Trp Val Trp Asn Ile Ser Ala Cys
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355 360 365

Ala Pro Val
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ggatc 185

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<212> DNA
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<212> DNA
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<210> 723
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cctccggaaa atccaantag agtaantncn ctctaattcg gggnaattgg nggggtnnat 60
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gnatcnanta gccgtncccg anatncaacg cccctacgtc 160

<210> 724
<211> 156
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(156)
<223> n=A,T,C or G

<400> 724
tnanccnata tacaccaaata tctgattcta aantcccacc caagggaaaa aagttgagaa 60
gaggcctttcc acttttctac taataaaaaaa atgcaccagc ccctaccann agtgnggaaa 120
acctccttag gcccttgnnt ggaacaancg aaaatc 156

<210> 725
<211> 347
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(347)
<223> n=A,T,C or G

<400> 725
aganggtnt atncatgctg tactcgcgcg cctgcagtcg acactagtgg atccaaagaa 60
ttcggcacga gagacgggtgc gcgtatggacc gagggccccca gcccggngagg cgccgccc 120
gagcccgccgg ncagacgccc catcagtagc gtccgcacccg ggnagccgcg gntctgcgcc 180
gagccgtggg cgccggccgag gggcgggctc gcctcccgcc gtccctcgca gctctgccc 240
gccccgagccc gcccgtcgcc cgccggccgnc ttgcgcgtcg gnccgcgcgg nccggnaaac 300
cgccgtcgagg tctggatgng gcanngcccg cnccntcgca tgagcct 347

<210> 726
<211> 162
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(162)
<223> n=A,T,C or G

<400> 726
ttgggtgggt tgggtgggg naaattncc cattgggtg ggttgggg ggnaatact 60
tcccgcctt tngtnccca aaganacnaa ggggagatcc cttnatagag gnagngcgt 120
ncntcncaac nacnngact ttgnccatgg ggagnaagg gg 162

<210> 727
<211> 120
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1) ... (120)
<223> n=A,T,C or G

<400> 727
gtgtgggtgg ggaattccat tgtgggtgg ggnnaatctc cgcttgcata aagnacaggg 60
gggtcnctt anagnnagg gggttccccc ccaccacttg nctgnccat tgngagnaag 120

<210> 728
<211> 130
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1) ... (130)
<223> n=A,T,C or G

<400> 728
gaccactgc agcgtnaac ttagcttggc ccgagctcg atccctagtc cgtgtgg 60
aattccatgt gtggagagag gggcaaatac nctccaanac ancncctca tgctcnacac 120
atattcgcac 130

<210> 729
<211> 182
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1) ... (182)
<223> n=A,T,C or G

<400> 729
cngactgctn gcgttaaac ttaagcnagg taccaacgg ggatnnacga ctantgatcg 60
gctggctgct tccagtcgt tanatttgcg aaaaagctga accncngccn gttaaggggg 120
annatgcaaa anatncatcc nnctgccccn taaactgntc tntccnaggg aaaaaangga 180
ag 182

<210> 730
<211> 678
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(678)
<223> n=A,T,C or G

<400> 730
cactcnact ccggacctag gcncttcacc actgctctt tcctcctctt cctccntc 60
ctcgccccctg ggggaccttc cccagtgacc atctcaactt ggctgaanc cactcgcccc 120
agcctgagg tggggctctt ggccttctca ccctcctcg ccccctcctt ggccgcacc 180
aggccaaacc ggggcagccg taccttgagc ttgtgtccgg cctctccctc cccctctgcc 240
acctggtaact cggcatggtt gccccggga tggcgagagc tccacgtcg gcaagtgagaa 300
gcagaaaagta cgctcgcccc ctgggggctg ctccctcagca ccctcgcccc ccacccttagc 360
tctggccccc agtgtggca acttcagcct cagcccaccc tcgcctgtgg cgcctcgcc 420
cgccctgtgcc tctcggtta gccccacgtc caactcaagc tggggcactg tcacgggtgg 480
catcttaaag acaccctcac ccaccagcag ctcaccacat gcaacctggg ctccaggcaa 540
aaaaagggtc acctggggca nctgaacct gtacctgctg tgccctctgc tgaanggaat 600
gttatctgaa cctgctgccc tgggggtact gcctcccaa aaccgggtca antccacctg 660
ttggaaaggna aatncccc 678

<210> 731
<211> 135
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(135)
<223> n=A,T,C or G

<400> 731
gagatccgac gtcacccct tceggcgccc caagacgctg caactccga ggcncccaa 60
atatcttgg aagagcgctc ccagccaaac acaatggaat tccaccacac tggnnntagtg 120
gatccgagct aagcc 135

<210> 732
<211> 660
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(660)
<223> n=A,T,C or G

<400> 732
gcttggtacc gagctnggat ccctagtaac ggccgcccagt gtgctggaat tcggctttct 60

tcaatcagnt nacgagctgc atggctcgct aacattgtca taattgctgg catagattttt 120
tggaaaataaa gaaaaaaaaat tgaagctgcc tatcaagttt tggtattatc aaaaacttcc 180
tacaaggat tttacttcaa ccatgttattt acaaataattt taatgaataac tttagagact 240
ttaattacaa aaaactgaga tagtaaaagc aagtaataaa agctgaaattt acttagctat 300
ttgataatta cataaaattat tatggtccat tcaacttttc tagtggttag tttatacaccc 360
aggaagactt tcctattcta ctaacattt aaaagtatgc taaccttattt tttaaacgc 420
tccactatta ggattttatg gcctaaaacg tgatacagtt cagtatcttgc atgtcaaaac 480
tttttaagca agtagggatt aagttcaagt gaatgtgatt ttctttcttcc ccagtaggg 540
cttctgaata actcagnaaa gctcacttcc attatcttac tttataaaaaa aatgctataaa 600
gacagaatgg gccgacgtgg nngctccacc tggatccacc tttggaggcg agnggcgaat 660

```
<210> 733  
<211> 836  
<212> DNA  
<213> Homo sapien
```

```
<220>
<221> misc_feature
<222> (1)...(836)
<223> n=A,T,C or G
```

<400> 733
aattaatgac ttttttccg ccctgccaag ctagttgtc taaaatataat gtaaaagaaaat 60
tagctactca ttttctggc cacgaagggtt cctaaaatgg gaagaagtgg agatctgacc 120
ttgttagttc taaaatacact aaactgggag tgccatggat ggcttcagg atgtcctgaa 180
tcctctataa ttgtatacaa aatcgtagt ttttaaaaac tgggtagag ctattggttc 240
ctcagagtct caggcatctt agaccccaa aaaggttaag gactactgac ttaaccaatt 300
aggtttgagt ggcattggct ttgaagaaaa gcagaggaaa gatatatttt ataattctgg 360
gcaacaaaaa agtggatgtg tgccagcatc ttagagtaga atcctcttaa aaggatagca 420
ctgcataatga actagtaggt ttaaccagt gcatatttag gcgaaagtgc tcattttct 480
gttagaattc ttttttattt gggaatgggc aagctttac agctttacc ttgccaatga 540
atacctggaa tttaaaaaat cttgttaggc atattgcccc taaagttttt ttccctagat 600
catatattca gtaaaatatgt ttgtagctt attcaatcc cccaaattcat tgagggttga 660
aacaatttga atggtttgag tgtagaagct aagttatttc tgttagaggct aaggcattt 720
ataccaanat atgttagact tgnngnccct gtaaccatg ctgtanacaa taggaattac 780
tgtatatcca catttaatt ttaacatctt ctgctttgnt gntgggttga gangga 836

<210> 734
<211> 694
<212> DNA
<213> Homo sapiens

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<220>
<221> misc_feature
<222> (1)...(694)
<223> n=A,T,C or G
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<400> 734
nagtnctatt tncactaaac tgngagtgc ttggatggct ttcaggatgt cctgaatcct 60
ctataattgt atacaaaatc gtgagttttt aaaaactggg ttagagctat tggttcctca 120
gagtctcagg catcttagac ccccaaaaag gtaaggact actgacttaa ccaattaqgt 180
```

ttgagtggca ttggcttga agaaaagcag agaaaagata tattttataa ttctggcaa 240
 caaaaaagtg gatgtgtgcc agcatcttag agtagaatcc tcttaaaagg atagcactgc 300
 atatgaacta gtaggttta accagtgcac attaggcga agtagctcat ttttctgtta 360
 gaattcttt ttatttggga atgggcaagc ttttacagct tttaccttgc caatgaatac 420
 ctggaaattta aaaaatcttg ttaggcataat tgccataaa gtttttttc ctagatcata 480
 tattcagtaa atatgttgt agctttattt caatccccca attcattgag gggtgaaaca 540
 atttgaatgg tttgagtgtt gaagctaagt tatttctgtt gaggctaagg gcatttatac 600
 caagatatgt tagacttgtt gttcctgtt accattgctg tagacaatag gaattactgt 660
 atatccacat tttaattttt aacatcattc tgtc 694

<210> 735
 <211> 126
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1) ... (126)
 <223> n=A,T,C or G

<400> 735
 ncnttggaaac nggttggacca gacttcaggc ctgtgcgcgc aatcggtgg aatctcggtc 60
 cgaattcggc acgagtctct ctctctctct ctctctctct ntctctctct 120
 ctctct 126

<210> 736
 <211> 165
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1) ... (165)
 <223> n=A,T,C or G

<400> 736
 cagaaggcctt taaaccggtt ngaccagact tcaggcctgt gcgcgtcaatc gtggagaatc 60
 tcgtgccgaa ttccggcacga gtctctctct ctctctctct ctctctctct ctctctctct 120
 ctctctctct ctctctctct ctctctctct ctctctctct ctctc 165

<210> 737
 <211> 125
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1) ... (125)
 <223> n=A,T,C or G

<400> 737
 ggnagccct ttaaccgttt gtccagactt caggcctgtg cgctcaatcg tggagaatct 60
 cgtgccgaat tcggcacgag tctctcttc tctctcttc tctctcttc tctctntctc 120
 tctct 125

<210> 738
 <211> 137
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1) ... (137)
 <223> n=A,T,C or G

<400> 738
 ggagnncnctt gancaggatg accgacttca ggcctgtgcg ctcaatcg gagaatctcg 60
 tgccgaattc ggcacagagtc tctctcttc tctctcttc tctctcttc tctctcttc 120
 tctctcttc tctct 137

<210> 739
 <211> 970
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1) ... (970)
 <223> n=A,T,C or G

<400> 739
 aggcttattt aggtgacact atagaacaag tttgtacaaa aaagcaggct ggtaccggtc 60
 cggaaattcgc ggccgcgtcg acggcccttn gtgccactag ntctttcatt cttccccccc 120
 atcaatcagt gaactttta gcctactcaa agctttgctc caatgcatacg gatttatgtat 180
 tgtggggatt tccagataat ataaatattc aacatgaata ttttaaatta aggcatgaga 240
 cattttcctt aactgagcat agccatgaac ctctcacgtc tgttcctctg tgtcagttt 300
 tancactgaa tacagcagcc ctcctaaaaag tccaggcagt gcacaggctc tgacatgtat 360
 aagtgacgtg ttgctatggt gattttgcag ctggccaaat agtcactggc tgattttacc 420
 cagcaggaga ttttgcaaa aatttcctgg gtgagagtgaa aatcaaactc ctatttgnt 480
 tctcctctgc aagctgnagt taagatggat taatgagttac ttttagatata attaactctg 540
 aagagaaaaat gggagaaaaag tgaggaaggt tgttggcaga agtcattgtc ggaatccttc 600
 tgaagggagt actgacttca cttgcaaaga cnagagacta naagacaatg aagttaaact 660
 tggcctgtct ctcatatgtat agatgctgag agtcaggntc agggaaaattt aattctgtca 720
 tacgcataatn ggattatgtg gtcatggatt tgttggcact aaccngctn taatcagnat 780
 aagaaaaatg ttttgtaga naaagaaaaat tatggcccag aaaaacctgg aanacttgga 840
 aaaaatgntn gggggccttg ggtggtggtc tnaaaaanacc ccctggggat ntttaaacca 900
 aaantgaaga agggaaaaat ntttccccnt nttttnttt tttgccccct tgggattggm 960
 ttttntttcc 970

<210> 740
 <211> 739

<212> DNA
<213> Homo sapiens

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<220>
<221> misc_feature
<222> (1)...(739)
<223> n=A,T,C or G
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<400> 740

gntgtcnaaa aagcaggctg gtaccggtcc ggaattcgcg gccgcgtcga cggcccttgg 60
tgccactagt tctttcattc ttcccccca tcaatcagtg aacttttag cctactcaa 120
gctttgtcc aatgcatagg atttatgatt gtggggattt ccagataata taaatattca 180
acatgaatat tttaaattaa ggcatgagac attttccta actgagcata gccatgaacc 240
tctcaagtct gttcctctgt gncaagttgt agcactgaat acagcagccc tcctaaaagt 300
ccaggcagtg cacaggtctt gacatgatga agtgacgtgt tgctatggtg atttgcagc 360
tggccaaata gtcactggtt gattttaccc agcaggagat ttttgcaaaa atttcctggg 420
tgagagtgaa atcaaactcc tattttgttt ctctctgca agctgnagtt aanatggatt 480
aatgagtact ttttagattaa ttaactctga agagaaaaatg ggagaaaaagn gaggaaggtt 540
gttggcagaa gtcattgctg gaatcccttct gaagggagta ctgacttcac ttgcaaagac 600
aagagactan aagacaatga agttaaactt ggctgtctn tcatacgata gatgctttag 660
agtacaggn t caggaaattt ttaattctgn catacgata ttggattatg tgggtcatgg 720
ctttgttgg cnccctaacc 739

```
<210> 741  
<211> 1171  
<212> DNA  
<213> Homo sapiens
```

```
<220>
<221> misc_feature
<222> (1)...(1171)
<223> n=A,T,C or G
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<400> 741

gccttggnggt gacactatag aacatgttg tacaaaaaaag caggctggta ccggccggga 60
attcgccgccc gggtcgacgg cccttnntgc cactagtctc ttcatcttc cccccccatca 120
atcagtgaac ttttttagcct actcaaagct ttgctccaat gcataggatt tatgattgtg 180
gggatttcca gataatataa atattcaaca tgaatatttt aaattaaggc atgagacatt 240
tttcctaact gagcatagcc atgaacctct cacgtctgtt cctctgtgtc agtttgtgc 300
actgaataca gcagccctcc taaaagtcca ggcagtgcac aggtcttgac atgatgaagt 360
gacgtgttgc tatggtgatt ttgcagctgg ccaaataagtc actgggtgat ttaccac 420
aggagatttt tgcaaaaatt tcctgggtga gagtgaaatc aaactccat tttgtttctc 480
ctctgcaagc tggtagttaag aagggattaa tgaggtactt tttaagaatt aaattaacct 540
cttggaaagaa gaaaaaatgg gggaaagaaaa aaagtggaaag ggaaaagggn ttgggtttgg 600
gccnaaaaaaa aagtccaan ttnggcntt gggaaaaat tccccnttt cttggnaaa 660
aggggggnnaa ggtaancct tgggaacctt ttcccnncct ttnggccc aaaaaaaaaac 720
ccanggggaa agaacctta ggnnaaggaa acccattttgg gaangggttt naaaaaccntt 780
ngggcccccg ggccctcctc caanaaggga aaaaaaaaaagg cctggaaaan gtaccagggt 840
ttcangggna aaanttaaaa ttcttgccca atancnccat aattggaaat tatggggggg 900
ccatgggcctt ttggtttggg cncttaaccc cgcnntttaa attcaaaanna aaaaaaaaaagng 960

gtttggaaaa nnaaanaaaa aaaatnaan ggnccnaaa aaaaaccctg gaaaacctt 1020
 gaaaaaaaaat tngnnnggggg gcnntttgt tgggggggtt tnaaaaaacc ccctnggggg 1080
 ttttttaagc ccaaaggggg gggaggggna aaanggtncc cttnnnnnn ttttnngccc 1140
 cccttggga atggnttant tcangggcc c 1171

<210> 742
<211> 739
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1) ... (739)
<223> n=A,T,C or G

<400> 742
 gntgtcnaaa aagcaggctg gtaccggtcc ggaattcgcg gccgcgtcga cgccccctgg 60
 tgccactagt tctttcattc ttccccncca tcaatcagtg aacttttag cctactcaaa 120
 gctttgctcc aatgcataagg atttatgatt gtggggattt ccagataata taaatattca 180
 acatgaatat tttaaattaa ggcatgagac attttccta actgagcata gccatgaacc 240
 tctcacgtct gttccctgt gncagttgt agcactgaat acagcagccc tcctaaaagt 300
 ccaggcagtg cacaggtctt gacatgatga agtgcacgtgt tgctatggtg atttgcagc 360
 tggccaaata gtcactgggtt gattttaccc agcaggagat ttttgcaaaa atttcctggg 420
 tgagagtgaa atcaaactcc tattttgtt ctcctctgca agctgnagtt aanatggatt 480
 aatgagttact tttagattaa ttaactctga agagaaaatg ggagaaaagn gaggaaggtt 540
 gttggcagaa gtcattgctg gaatccttct gaagggagta ctgacttcac ttgcaaagac 600
 aagagactan aagacaatga agttaaactt ggcctgtctn tcataatgata gatgcttgag 660
 agtacaggn t cagggaaatt ttaattctgn catacgcata ttggattatg tgggtcatgg 720
 ctttgggggg cnccctaacc 739

<210> 743
<211> 610
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1) ... (610)
<223> n=A,T,C or G

<400> 743
 ctgtccttat ttcttagca aaaattccc aagagaagaa ttgctggat aatgcacatt 60
 taaaattttt atagacattc ccaaataatta tacctgttt tgagacctt aattcctgtt 120
 gtcaaatgc cctatatatg gagtaataaa cacgattna agaaatgagg actaaaaaaaa 180
 gattatataat aacccaacat aaaggcaacc tcttaggcgt tgacagaaac tgacaacttt 240
 ttatctgtgg gtgcgtatcca ttataagtaa cctgagcacc ttatttttc tttttaaact 300
 ctaggttagga taccggaggt ccacaaaattt ttccataagaa atatttttc tctgccctat 360
 gagatttaa aaaatattat actgcttcaa ttgcatcaaa agaaatggac cctaataatct 420
 atgatgaagg atttggagtt agaagacctg agttcaatt ttggcatggc tggttgtcta 480
 gctctgngat cttggacagg tcaattgact tggcttaatc ttctcatcca ttttagnggag 540
 acagcaccac tattcacagg actattgncc gaattaccag acaatagcat agggaaaat 600

ataangcctt

610

<210> 744
<211> 127
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(127)
<223> n=A,T,C or G

<400> 744
ttcacctccc tggaccgggc cccccttccc cggggcggncc ccccgggctg caggaattct 60
gcacgaggga gagagagttt gagagagaga gagagagaga gagagagaga gagananaga 120
gagagag 127

<210> 745
<211> 458
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(458)
<223> n=A,T,C or G

<400> 745
gatatcccg gattcgccgc cgcgtcgacg tggcctctag tttgtcctgg tccaaagcag 60
ggaagctggg ctacgtcctg cccaggtcag ctttaggtta agggctgcct gggggaggga 120
acttcctggg cttcgggtc tctgtcaact ggggtggctc ctgtggccca gaatccctg 180
gagaagggtc ctacttggaa cgaagggtgca gggcagcagg gcctgaggcg caggagctgg 240
tggaggctcc cagcacaggt cgccgccccca gtcacatcac tgctgatgg 300
ggggagtttc ccccgagaat gggaggtctc acagtccccg tgctgcaatg ctgtcggtgc 360
actgngncng caatgtgctc atggncactt gcttttctc tgtggcccg gccgatttat 420
ccagcanngc acccctcttc tnctctccgg anaaagcc 458

<210> 746
<211> 893
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(893)
<223> n=A,T,C or G

<400> 746
aagcaggctg gtaccggtcc ggaattcgcg gccgcgtcga cgtggggagt tagctcttg 60
gaccgggtca tagagtaagt catcgataga gcatttgctt gatggggact tccagaaggc 120
canngaaagt cctggccact tcctgggaa gcccacccgc acgtgggtg aggtccccca 180

natggaagca gctgtgtatg cagggagggg gcagaggctg ctgccaatgg gcatgtccct 240
 tacctgaaag ggccacctct ccaggtgaca tgtctgggg gagccggggc cgctctgc 300
 ggccagaggc gtcagctca ggccacacca ggcagggcac ctcccaacct ggacaggtgg 360
 ggaccaaggt ggcctggac aaaactctct gtgttgc 420
 gagtcaaccca caccccaagtc acatgggtgc cacacngcag gggtaagga ggccggccc 480
 ctccccctca gacgtccctg ggcctctgg agtcagcaag gacgaggacg gcattgccct 540
 tcgagacagg aaggagtg 600
 gagagggggc tacttgc 660
 tgagcacctt gcaaacaacag tgcacccacc 720
 tcccatttct tcggggggaa acncgccc 780
 acctgggggn cggccgacc cctgtngctt ggnnagccc tccncccagg tttctnnngc 840
 ngccnttaa ngncntng nttggccct tggccncc 893
 tncgctttc cca

<210> 747

<211> 738

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1) ... (738)

<223> n=A,T,C or G

<400> 747

gatatcccg 60
 gaattcgcgg ccgcgtcnac gaagcacaga cctgngccct gctctcatgg 120
 ggcagactgc catttgtcat tnattactga aggaaaggga tcctcagttt gcttggac 180
 atttcaaatt tgaggtgaga gttggataag taagaataaa gctgctttc aaagagatga 240
 atatagaaaa agaaacaaga tacagnctg gcagaaggc tgggaggaag gggaaaaggt 300
 aataaagaat gaaagagtga gaaatgtgag caggagctga acacagaaaa gttcagngac 360
 agaagcanaa ggagggaga 420
 agggaggagg gtcccttca cagaggctca cgaggatgct 480
 ttatgngtgc catgcagtcc atgttcagga tgtctgc 540
 ttanctctc actttctaa 600
 tanaaatttg gatacttact gatcctacat atgtAACAGG gagagaaggt gaatttcaa 660
 gcantaaattt gaaaattgt tcacaatttc atttttaaa aaaaggggac taacagaaga 720
 agaggttaat gtggtaatta taggatgnct cttgcacac atgaatgnat ctggtatcat 780
 ctgagtggga ggggagctgt cttcctgacc caaaaggatc ctttcgttan ccngnactta 738
 ngtcccaaaa ctcaccacc ttggagaaat natttcctt tgggggtn 738

<210> 748

<211> 647

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1) ... (647)

<223> n=A,T,C or G

<400> 748

ctntgtggcg gtggctgtct cattgggtg gacttttg gtcgttagaa cctggatng 60
 aggtcgagag taagacggc tatttagtgc cgcatcg 120

agggcctctg tctcogctgc gctcgccctaa attggtatgg ctcgacttgg aaacacggtt 180
 ctaacacgcttggtagcgc ctttgcttagc atgtgaagga cactggccctt accaagaag 240
 attcgagtcg ctcctccgg tatcgttcac ggaggcgata ttactcttc ttactacggt 300
 tacttcgaga ttgtctgtga agttaagac tactaaaaag agtattaagc ctatcggaa 360
 ttagcttagat cgacacgcta aaaccaaggg caatcggcgg aaatatagag gcaccaataa 420
 tagggcctac agaaggcccgg agggtagac tcacgtttaa taccggccac gggagaaata 480
 aaaagataaa gtatacatcg tttagcggc ctcggaagcc ttcggctta atgccaagga 540
 gtcgaaagca tcgtcggcga gtaataaaact ccacatcgcc gagactatct acgacgccc 600
 ccttaanatc cgtaaattac tcccgaaag agtatttagg cggtct 647

<210> 749
 <211> 642
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(642)
 <223> n=A,T,C or G

<400> 749
 ctntgtggcg gtggntgtct catttgggtg gacttttgg gtcgttagaa cctggtatgc 60
 aggtcccgccgg agcgtggct ctcgtcggtt atgttggggg ttgggtgtt gccgggtt 120
 tttggttctg ttgagcgtag tgtgtttagaa ggttagcggtt cgtgtcttgc ttgtggttt 180
 gtgttttaggg cgggtggggg ggttgttgt tagctgttgtt atgtcatatt gttgggtttt 240
 ctgccctgtt ctgtttgtcc ttgggttattt tggttgttac cccgcctgtt tggaagtgtt 300
 gtggcaggggc gggaaattaa gtgggagagt tgtggaccc gtgggtttt gttacgttgc 360
 gctttgtcg tggcggtgg cggcgcgtt gataattttaga attggatacg gagttataaa 420
 tacttctagt aaatggggac ctatgtctt acttcccgga ataggatct atgcgaagtc 480
 cttaggatag tctttgataa gttaacgccc cacgaccctt aaattataca cgattagacg 540
 cataacgact cctccaggaa agataaaagaa tctcacatat agaacgggac cccatacagc 600
 tcggatagga aacaagagaa ctaatttng ttaaaaagac tt 642

<210> 750
 <211> 639
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(639)
 <223> n=A,T,C or G

<400> 750
 tttgtggcg tgggtctca tttgggtgaa ttttgggtc gtaggttaacc tggatnag 60
 gtatagatgc cgattggtcc cgacgagcgt cacgataaat tcggtagttt cgccctttt 120
 agaaggcgct agtactcgga acttcacttc atctcggtt tagtttgg cgtatatacg 180
 cttctccctc gaagacttagc cgacatccatc gttccctagg aatcgtttcc gcccctaaga 240
 atcccgagagc gagatcccgaa aactagagga accttagaag agtctgtatcc ccacaaggac 300
 cccacagtca ttccgggaaa atcccttaga ccatacggtt aggattcccc cggaacccgg 360
 agcaaagctc atgattcccc acaccgcgag agcgcctata accctatccc atttctcgg 420

gttatcgagg atattacgat caagccgaga gaaccgctag aaccgcttc ttgcgtttct 480
 cacggAACCT ataagttagaa agagaaaactc aggtcttaag ggggcgttc ggctaacgaa 540
 acttctactt acgaagagag tatctagaca ttaagtcata aaaatccact acgcacctcg 600
 tgtacgatat catcgggagc gttcataga cggtgtccg 639

<210> 751
<211> 637
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1) ... (637)
<223> n=A,T,C or G

<400> 751
 cttttgtggc ggnnggtgtct cattttggtg gatttttggg tcgttaggnaa cctggtatng 60
 aggccagctct gagccccccc cccccccccc ccccccnccc cccccccctt ggnngttggg 120
 aanacggtgtt atacctaaat cgagtgnntt cattaaaagt agttgattac nccctaaaat 180
 aanaanaggg ctgcgtcggg anaatacggt aagganaagt ctttntggca tcataanaat 240
 actggctcgg gtcctaananat ntttaaggng gtcnccgagg gtnttcatac cgataanaaa 300
 cgttttccta tcggcaacgg gcttacctga gggnggactt ctcncggngc ggnngatnn 360
 acgaanacgt agaggattnc cgntactnt tganatcacn cgtatcatac ttgttaagcat 420
 aattntcctg aaaagtgtta taanaataacg cncgcatatt cgcttttcg tccttagggat 480
 gcttaaatgg cgataactgct atagcgggtg agcgttgggtt ctcgagnaan aaagcgtgtc 540
 ctaatcgctc taaggnttta aggnncgttgg tttaaaaata nccttagaaa cctcgaggcg 600
 gatactgggtt nttnnttaac gaaacaaaagc accccnn 637

<210> 752
<211> 644
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1) ... (644)
<223> n=A,T,C or G

<400> 752
 tntgtggcgg tggtgctcat ttgggtggat ttttgggtcg taggaacctg gtatgaggc 60
 ttgcgagttg ttgggtgtc ctgtcggtcg gtgggtccct tttgagtgtga gtttgcctt 120
 tgaggttgtt agctgctgtt cggttgtgtt cgttagtgc tttgggtgtga gagggttatg 180
 gtgggtgtta cgggtgtattt tcgcccgtgg tcgcgggtt ggggtggtcg tcggttttgt 240
 ggttcatagt agtcttctgc gttcggtggt gcgggtttgg gtgagtagtt tcgttcttgg 300
 atgtcccatt gacccgcat aatctaagta agggtagta gaaacctctc cccgatagac 360
 acaaccgtcg tccactaaag acctcgccctc tgattttaa aaggaccga aaaacatccc 420
 ttcaacggaa aaaacggaaa aaaagtcaacg gaattcaaag aagccacggg agagaaaaaa 480
 gaactaaagt tagtccgtca ttatatgtct cctcgagga ggaagcggcg gtggcggaaa 540
 atgaggcgggt aagaaagacg acctctatcg gcggcttang ccctaaaagg gcgatacc 600
 acgggatgtat aaggacccta ggacgcctcc ttctcggtatc gtcc 644

<210> 753
<211> 635
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(635)
<223> n=A,T,C or G

<400> 753
ctttgtggcg gtgggtgctca tttgggtgga ttttgggtc gtaggaacct ggtatgaggg 60
aatcagctcg accccccccc cccccccct ccgaagcaga gccaaaccca aagtccaccg 120
actaccgcag taaaactctcg gagggtagaa taagaaggag taggtcctag ccaatagaag 180
tagttccgag ccgttaggac agcggacgga acattnaaga aagagcctat attagggagg 240
aagtaacgtt cctcttcgg agctcttaa gggtagtcc cagaacaagg gaagaggacc 300
cgtcggctat tgcccggtcga tacgggtctc cacggngagc ctaggttcga ggatagggcc 360
gctcgtaaaa ttatacggtt tccgagaaac gttccgtag accgggtcct aaatcgccg 420
gagttatnng agagggatcc ttcggaccct agggacagag agaggagaac ggaggttaca 480
ggaggagaac gtntcctcnc tagttttctt tangtcgaaa aatttcttac cgatagggtt 540
cctagggtcg gngaatttac gttcgaaaa acggtagtnc ctaanggntg ntatnnggg 600
tagtatcgaaa tcgttacaa ntctccgtc ttntg 635

<210> 754
<211> 721
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(721)
<223> n=A,T,C or G

<400> 754
accggatnng ttncgtgacg cgtgactgct aataaaaaag atggantgcc atctttttt 60
ttnccttgct ttatatatcc agcagcaaaa caaaattgtt ctgcnggct ataaaatttg 120
gcttgtgagt cttgtacaca actcaggagt gtgacacagc taccagctt cctcttaact 180
ctcaaggaaa gaaaattcaa gttctgtcta ggctcactct gtaaagtggg aaacttgctg 240
gttttgttagg cttttttcc cttctttcc ctctctcagc ttctccctgc ttctcagaan 300
atggagttgt gatgcctgca acttacaaa tttatctatg aatcagattc cagtgggaga 360
cccctaaagc agagggagaa taaggagttc tccccatgtat gaaaaatatac caaagacaag 420
gtttcatgga gcaaaaattt ctggctagat ttgggttgta agtggatccc tccccactgc 480
gtgtacactt tatctgtctc tttgcttctt ccccacccctc tttcccaagct ctctctctgt 540
ctctctcttg ntccctgac cttttttct tcccantgca tactttttt tttccctttt 600
ttaatcttct atantcttaa ncctaccaan gggccctcnt gannaattn tcacccctga 660
atagggatt ctntangccc tgagaatttc nttatcanaa aaatattttt taaaagcatt 720
a 721

<210> 755
<211> 721
<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1) ... (721)

<223> n=A,T,C or G

<400> 755

accggatn~~t~~ ttnctgagcg cgtgactgct aataaaaaaag atggantgcc atctttttt 60
 ttnccttgct ttatatatcc agcagcaaaa caaaattgtt ctgcngggct ataaaatttg 120
 gcttgtgagt cntgtacaca actcaggagt gtgacacagc taccagctt cctcctaact 180
 ctcaagggaa gaaaattcaa gttctgtcta ggctcactct gtaaagtggg aaacttgctg 240
 gttttgttagg cttttttcc cttctttcc ctctctcagc ttctccctgc ttctcagaan 300
 atggagttgt gatgcctgca acttacaaa tttatctatg aatcagattc cagtgggaga 360
 cccctaaagc agagggagaa taaggagttc tccccatgtat ggaaaatatac caaagacaag 420
 gtttcatgga gcaaagaatt ctggctagat ttgggttgtt agtggatccc tccccactgc 480
 gtgtacactt tatctgtctc ttgccttcc ccccacccctc ttcccagct ctctctgt 540
 ctctctcttgc ntccctgtac ccttttttcc tcccantgca tactttttttn ttccctttt 600
 ttaatcttct atantcttaa ncctaccaan gggccctcnt gannaatttn tcacccctga 660
 ataggggatt ctntangccc tgagaatttc nttatcanaa aaatattttt ttaaaggcatt 720
 a 721

<210> 756

<211> 873

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1) ... (873)

<223> n=A,T,C or G

<400> 756

ggaagaatac agtaagttt~~t~~ caaattaaaa tttctctatt tttctgttat ttattcattt 60
 ggaaactgtc agcctgtctc tttcactttg ggcaagtgaa agcaaagacg tccagtccta 120
 tcagcaatta ggctgaaagt caacgc~~a~~ag ctggcggca agggctggc tgagtagagg 180
 ttcccttaggc aggcaagaga gagactccca ctgcataactc ccagctcggc aactgcctga 240
 atgccaatga gcactcatta taacccgccc tattttatag gatttaattt tacacttcag 300
 gcttaatcag tctgaaagtt aaactgacag tgtaatgtt~~t~~ cggaatcaat gacatttagg 360
 ctttatgact ttgtagctga atatctatgg gctatatttc cattctaaca gtgatatcc 420
 gttccagaat ctcatttctt ggtgatggca cttcttagtg gagcagtc~~t~~ ggttaacagtc 480
 cacaccatt accatgtggg tgctttacag catactgacg gaaggactga ggagccaccc 540
 gaggcaggagt tcctctcagg gaggacgctg acacttccac agctgcctan gtatggc~~cac~~ 600
 ctgatgccaa cgaanaaccc aaagcgctt cccttccaga tggaa~~g~~ctgc cccacactgg 660
 gctgacagaca tctggagctg ctctggctca aatcccggaa tcgcacanct cctancgggg 720
 gcgtttanag atcctcnggg ccagctaccg accactttt~~g~~ acaagggnct taggagc~~gat~~ 780
 aactagnctg gcgcgttaca cncggatgga acgtcttgg~~a~~ cttgagac~~t~~ cttgggggan 840
 atggcncccc caaataantt gggaaaantn ggg 873

<210> 757

<211> 782

<212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1) ... (782)
 <223> n=A,T,C or G

<400> 757

ggcccctcga gggatactct agagcggccg ccgactagtgcg agctcgatcg cgtatcccg 60
 ggatttgaga ccaggagaca gctccagatg ctgtcagcccc agtgctgggg gcaggcttcc 120
 atctgtgaag tggagaggcg ctttgggctt cticgttggc atcaggtgcc catacctagg 180
 gcagctgtgg aagtgtcagc gtcctccctg agaggaactc ctgctccggg ggctcctcag 240
 tccttcgctc agtatgtgt aaagcaccca catgtaatg ggtgnngact ggtaccatga 300
 ctgntccctt aaaaggtggc cttcccnaag aaagagaat tcttggacna gggatttcac 360
 ttgnnttagaa atggaaaaaa ttacccatata gaatttcgn ttccaaggcn tnaagnncta 420
 aaaggccctt gattcccgaa ccttaaccct gggcagttaa cctttcaaac gggataaacc 480
 ctgangggga aaatnnaatc cttaaaaaaaaa ggggggggtt naaggagggc tctttggctt 540
 tcaggcantt gccaacacctgg gaaattcana ggggaagtnt tttttttgc ctgccttaggg 600
 aacctttact taaacnaacc cttgnccccc cattgggggt tgactttcan cctaattgct 660
 gaaaggaccc ggccgntttt gnnttcctt gncccaaagg naaanaaaacg ggtgccantt 720
 cccangggat tantcccgaa aaatttggnn aattttntt tgnaactttt tgggtttttt 780
 cc 782

<210> 758
 <211> 647
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1) ... (647)
 <223> n=A,T,C or G

<400> 758

ntttgtggcg gtgggtgtctc atttgggtgg actttttggg tcgttaggaac ctggtatnga 60
 gggaaagagcg ccgtcggtcc gagtagacta tggagtagta tagtcttcgc gccttctcgg 120
 gcggcgcccc tattctctcc aaaggcagag gtccttagtc gacctcgctc ccctaggtta 180
 ggaacagccg tcgaatattt tagttcgtc gaggcttct tccgagctct acgcctaagt 240
 agctccgcga gcaaagtatac ggtcattttc ccctatccat cactcccta agtacgcctc 300
 attattccgg aaggcaagag gccagcattc ctcccttagag tagaggtag gtacctccgt 360
 cgcgtccgc gaaagggcag agcttcgtgt ctccctccg cagcagctt acggctacg 420
 taggcgttct cgatctttc acggaaatcg ggtccggga gggcggcggaa aaacgtcgac 480
 gtctcggtca ccgtcaccgc cccgaacaac tagggctt ccgcttcaa ctgaggaacc 540
 ccgcacccct cattagcgct tacgaaatcg gggangtgat tgcgccaatt cgtagcctt 600
 cgataattat tctctattag cggtcctatc tcgcgtttc gatttat 647

<210> 759
 <211> 657
 <212> DNA
 <213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(657)
<223> n=A,T,C or G

<400> 759
ctttgtggcg gtgggtgtc atttgggtgg actttttggg tcgttaggaac ctggtatnga 60
gggctctata gaaaggcctct tgtctttaga tacgggcttt ctggtccttc gttcttggaaag 120
tgttagtagta ggtactgcgg gaaggcgaag agtcctttca aggacgattt acttaagtgg 180
gcttattctta tagttcccttc gggacataag gtcggtaacga tctatactgc gtggaaagct 240
gataggttgg gacttaaggc gaataagaag gaggcggcgg aggtcgcgt taccgcagag 300
atattattta cggcggccgc gggtaaccgcg ggtcatgcgg aaattttctg aggttcttgg 360
attcctaaga tcgctcccgt cgagtatact agcgacgaac gtaagagtgc cctcacaaga 420
accggtaacaa actcaagaag aagttcccat taagcatcgt aagaaaacggt aggacgagga 480
cggttaagaag taatcggaga aaggatcccta gtngttacga agaagcatcg tttagctact 540
ttgcgttacc gtttatattt agacgtgttc cgtccttctc cgtgttana aaaaagggttt 600
attccgacgg gagacttagg cgaatggagg gttccgcggc tganaatcgg ancgggg 657

<210> 760
<211> 644
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(644)
<223> n=A,T,C or G

<400> 760
ctttgtggcg gtgggtgtc atttgggtgg actttttggg tcgttaggaac ctggtatgna 60
gaaaaagaag taaggcctga agcctatotc cgaccgtatt tatttcgcag aagacggaac 120
tacggacgtc gttaaccccg agtagcccc gtaagaaagg actaaagcga atggaaaagt 180
cgggattcc ggcggagggg cgccgattac taaaaggagt aagagtaaga ctattgcgt 240
acttgaggcg ttccctctta aaaggcaccc gaaacactct attaaaaaac accccaagaa 300
gaacaactca tgcgatccgc cgtgtgcagc cgtcaatagt aaagagagcc atgaaccatg 360
ccatccttag accaatttagg atgaagaaga ggaggaagat gaggacccaa ccctacccac 420
tcggaaaacc ccgcacgagc ctccgaacaa aatccggaa taaaaacggc ggcccacttc 480
cgcactctcg tagcgcggac cgaatagaaa accgaaaact acagctaaag ggtcctttcc 540
ggcctgttat ctaccaccc gcaatccgt cctccccccc cctcgtccaa aaaccctaac 600
ctctgcggca acattagagc agaaggagag ggcgatccct tgan 644

<210> 761
<211> 647
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(647)
<223> n=A,T,C or G

<400> 761
 ctttgtggcg gtgggtctc atttgggtgg acttttggg tcgttaggaac ctggtatnga 60
 ggcgggtact ctctggata atcgtataa gtgtgtaaa attggggta agagaaagtt 120
 tcattataag aagtggaaagc acgagccggg gtgttagtc gtaatatta agaccgttt 180
 ttgttgact tatatagttt gcgcgtggg aggcaataag aaacattgcg ttcgaggcc 240
 ggtatgcgggg aaccctcttc ggggtctaga ggcgcgcatt tgcaaaataa ggactactga 300
 cgccgctcat aacgtactca acaatgatc ggcctgcatt aagatttcgg cgaagaaccg 360
 tactgcgtct actgatagta tattgcattt atagcggcat gagctttatc acgtgtcg 420
 ttccgggttgt aagaagggag ttaagtcgtt cttcgaggaa gaagagaccc caaataaaaa 480
 atgactcaaa aaaacctaga agaaacacga cgaaaggaaa aagaacgtt aaactagtag 540
 ctcttcggan gagtagcctt agtaggttaa gtcctccgtg cgtactgtcc taaggtttgg 600
 atagcgcgtt tgaatagacg gtcacgcgtc agaaggtaaa aanccgg 647

<210> 762
 <211> 628
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(628)
 <223> n=A,T,C or G

<400> 762
 cattgtgttg gggtaactga gcccacttt ttccagattt tttgtaaaat tgtttcgc 60
 tgtgttccct ttattcgctt gtattaatat ttgcgtatg gattaaacaa atacttggtg 120
 ttgactgtca gtcttagagg actgactaga agtagtttc atttgggct cagggaaatac 180
 ctactttata tttctagcta attagggaaat tcattttca gttaggttgg tgtttgggtt 240
 caggcactcg ctatctatgat gacctaataat gctacttaat ttctgagttt tggtgtccat 300
 ccctgttagga ttgttgcggg gttaaatgaa attgtgtata tttgtaaagc atttacctca 360
 gtgcccgacat tgcacagag tagattatta ggcttgctct tatttctgtt attaaattta 420
 gtgtcagatt agcaacctat agctacttct aaagctgctg ctgctttctt tgtttaggt 480
 taggaagaaa catgctggac agtttgccaa atgagagttt catgatgtgg cttgtggaa 540
 cattctaact tggaaacttgc ccatttccag gactttnggg ttcnagatt tttggggata 600
 gatgttaaggg ttaaaaaaaaa cngaaaaac 628

<210> 763
 <211> 147
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(147)
 <223> n=A,T,C or G

<400> 763
 cattgtgttg gggcagagat aaataattcc tctgaaaagt gttttattgg aatttcaa 60
 gaaaagctaa ctggataact tacagcatgt ttctgcctt aatctctt aacaggcctc 120
 ttttttttat gcacaccacc ttcnngc 147

<210> 764
<211> 146
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(146)
<223> n=A,T,C or G

<400> 764
cattgtgtg ggtatgtttt ttgaaggcag gtggacagga tttgctgatg ggtaaatggc 60
agagtttaggg ggactgttag aacagagaaa ganatcatgg ggttggggtt gagtctgatg 120
nnnaacttgtt gccgnntgct cagtat 146

<210> 765
<211> 129
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(129)
<223> n=A,T,C or G

<400> 765
tncncgattc gntnctagcg tntacactna tgtcttgta ccgagctcg 60
ccagtgtggg nggaattcca ttgtgttggg gcaggaggng ctggngtac ngtgcggctg 120
nagaggcgg 129

<210> 766
<211> 175
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(175)
<223> n=A,T,C or G

<400> 766
cattgtgtg ggccttagtcc gaataactttt agtaacttca gacagatctc ctcatctttt 60
tctggggctt ggntttctc ctttgtanaa tgatgcctt ctgtggttt gtcatttcta 120
acattctgtg ngtgatgagg tgtatattcg anganctcta tcnccanagt actct 175

<210> 767
<211> 602
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(602)
<223> n=A,T,C or G

<400> 767
nnntttaaaaa nctgtnctcc ccgcgggtggc ggccgctcta gaactagtgg atccttcca 60
cctggtttgt ttcagtggt taatcctatt agtacgtca gatataggt caggatata 120
ggtcagaac ctgtggaatc agccaatttg gcttgctcat ttacttaat aaggcccatt 180
aatgagttagt agtacaaagt tcaagccctg ttgagggtct gcattaaact ctcagaagta 240
tttagagtgt gccaggagcc gcgaaaggctt ggttcgggtg gtggcgggaa ctgtattaga 300
gtgctaggca cggcgcgaca aagtctgtcc aaccaaaac ggtgctgagg cgttgggtgt 360
gagctccagt actcagaaaaa gcatctcagc aggtactcaa cagatcctca ggggcttggg 420
ggcccagcac tggcagttagt ggcatgaaag acataaaagg gcactacctg tgggtatTTT 480
ctgttctcca aggaggaagt agcaaaaatt aggacgctgg aatatcctat gtttagcaa 540
tccccagaaca actgatgctc aacaaatacc acacaaaaca aatttttaa aatttaatct 600
ta 602

<210> 768
<211> 671
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(671)
<223> n=A,T,C or G

<400> 768
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gcctttcca tgcttgctt atgcggctt cagcactgaa gaacagttc aattgctagc 240
caaccagaga gcatgatcaa accaaacaag ttccctgtt cagaaaaaac aggttttagg 300
taactgaagg gttaccagg actgattcca caatcttctc tgtaaaanat ttctgcctat 360
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nggggccccn ttatnaagct tttcaggcct tccccttcc atagcattgg tggatacaa 480
gaaaccttta aacagcaacn agctatcnag gccccaaaagg aaagtaatn tgattttta 540
nagattccgn aacaaaaaaaaa tggctgggtt caaatacnac cttctttta aaatggnttc 600
cttattaaac ntttttttt ttaattttt ccccatggtc ntgatnttng ngcttccgcc 660
canaaaatng n 671

<210> 769
<211> 877
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(877)
<223> n=A,T,C or G

<400> 769
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ggtttgttct tcacttgct aaccctctt ttacttaagg acaccttgaa cattccctcc 180
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cctttgacca tgacatcaac agtgctccaa attatggggt accgtattag cctatgtctaa 360
tcttgatcag aatccttacc tcgggtgttattt gaaatttatctt atttcggtcc tgcctcttta 420
aagtccagggt ttgccttatac tattgtctaa caccatgcag taggttaacat gcagtaggaa 480
acatggcatt aaattatttg ggttcaaatc ccagttatgg tgtgttaatg cctaccaggc 540
cgtgaggcac ctgctaagca ggttgcacgc atcatttggaa ttcacaccac ccttttgcaa 600
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agtgcatttc atatccccctn ctctgngggg naaggtccct cnccnggaga acnnttaaaa 780
caatcatntc tngggggntt aatgcttcc nccccagttgtt ggtncactgc ngccacgagt 840
cccancact agtcccaangt ctgtcatgaa ccancccc 877

<210> 770
<211> 874
<212> DNA
<213> *Homo sapiens*

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<220>
<221> misc_feature
<222> (1)...(874)
<223> n=A,T,C or G
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ccgatgaga ggttaacagta ttttactgat agtaatcta aagaaggagg ctaaataaaat 180
tgcccaattt cgaacagtga gaggaagaat taggattgaa acacatatag tggcttcaga 240
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cctctcggt gtccctttt tttagctatt tcagaagcac actgggtgcaa tattttacga 660
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natgaanatc ctgttatttc atatcttgat tggagctgct taattaaatg accatttttta 780
aatttgggtt gattccnnngc aaaaaaaaaaagtt tnttnttgg a tggtagggggc tcnnnaaagnc 840
caaaaaccccc caaaaattttt nnttgggaac ccna 874

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<210> 771  
<211> 156  
<212> DNA  
<213> Homo sapiens
```

<220>

<221> misc_feature
<222> (1)...(156)
<223> n=A,T,C or G

<400> 771
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gtgtggtgga attcgccggcc gcgtcgaccc cgagcggtcg ccctttttt ttttttttn 120
ngttttttt aanaattcat tgggtattta ttattc 156

<210> 772
<211> 586
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(586)
<223> n=A,T,C or G

<400> 772
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tccagatatg aaacttaccc ccaagctatgg tcttcttattt gttatTTAAT ttcttaggcca 180
attttttcca cttgaatgtc agtattttaa ttcaaaagtca ccttgcctcaa ataccaagtc 240
atcaacttac cctcaaaatata tttcttattt cagaaaatct acatcttata atggtagcta 300
ttttatccct gcccctgct ttttctttt atatttaattt aatttgntca tccagcaaatt 360
gcttattttag caggattttgt aggctaaaca attctanact ttaaggggac acagnttgca 420
aaacaaaatc ctgccttgna tggataactta tgnnatggng ggatacagac aatcaacata 480
atgangngca tcataatataa tggtagtagnan aatgataagg gntttggga aaaaaatgca 540
cccanccaan anggattggg aagtggangg gangtgcang ggangg 586

<210> 773
<211> 2983
<212> DNA
<213> Homo sapiens

<400> 773
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<210> 774

<211> 3064

<212> DNA

<213> Homo sapiens

<400> 774

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<210> 775
 <211> 684
 <212> PRT
 <213> Homo sapiens

<400> 775

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Asn Gln Asp Asn Ala Val Ser His His Thr Trp	Glu Phe Gln Thr Ser	
20	25	30

Ser Pro Val Phe Arg Arg Gly Gln Val Phe His	Leu Arg Leu Val Leu	
35	40	45

Asn Gln Pro Leu Gln Ser Tyr His Gln	Leu Lys Leu Glu Phe Ser Thr	
50	55	60

Gly Pro Asn Pro Ser Ile Ala Lys His Thr Leu Val Val	Leu Asp Pro	
65	70	75

Arg Thr Pro Ser Asp His Tyr Asn Trp Gln Ala Thr Leu Gln Asn	Glu	
85	90	95

Ser Gly Lys Glu Val Thr Val Ala Val Thr Ser Ser Pro Asn Ala Ile		
100	105	110

Leu Gly Lys Tyr Gln Leu Asn Val Lys Thr Gly Asn His Ile Leu Lys		
115	120	125

Ser Glu Glu Asn Ile Leu Tyr Leu Leu Phe Asn Pro Trp Cys Lys Glu		
130	135	140

Asp Met Val Phe Met Pro Asp Glu Asp Glu Arg Lys Glu Tyr Ile Leu		
145	150	155

Asn Asp Thr Gly Cys His Tyr Val Gly Ala Ala Arg Ser Ile Lys Cys		
165	170	175

Lys Pro Trp Asn Phe Gly Gln Phe Glu Lys Asn Val Leu Asp Cys Cys		
180	185	190

Ile Ser Leu Leu Thr Glu Ser Ser Leu Lys Pro Thr Asp Arg Arg Asp		
195	200	205

Pro Val Leu Val Cys Arg Ala Met Cys Ala Met Met Ser Phe Glu Lys		
210	215	220

Gly Gln Gly Val Leu Ile Gly Asn Trp Thr Gly Asp Tyr Glu Gly Gly		
225	230	235

Thr Ala Pro Tyr Lys Trp Thr Gly Ser Ala Pro Ile Leu Gln Gln Tyr		
245	250	255

Tyr Asn Thr Lys Gln Ala Val Cys Phe Gly Gln Cys Trp Val Phe Ala		
260	265	270

Gly Ile Leu Thr Thr Val Leu Arg Ala Leu Gly Ile Pro Ala Arg Ser
 275 280 285

Val Thr Gly Phe Asp Ser Ala His Asp Thr Glu Arg Asn Leu Thr Val
 290 295 300

Asp Thr Tyr Val Asn Glu Asn Gly Lys Lys Ile Thr Ser Met Thr His
 305 310 315 320

Asp Ser Val Trp Asn Phe His Val Trp Thr Asp Ala Trp Met Lys Arg
 325 330 335

Pro Asp Leu Pro Lys Gly Tyr Asp Gly Trp Gln Ala Val Asp Ala Thr
 340 345 350

Pro Gln Glu Arg Ser Gln Gly Val Phe Cys Cys Gly Pro Ser Pro Leu
 355 360 365

Thr Ala Ile Arg Lys Gly Asp Ile Phe Ile Val Tyr Asp Thr Arg Phe
 370 375 380

Val Phe Ser Glu Val Asn Gly Asp Arg Leu Ile Trp Leu Val Lys Met
 385 390 395 400

Val Asn Gly Gln Glu Glu Leu His Val Ile Ser Met Glu Thr Thr Ser
 405 410 415

Ile Gly Lys Asn Ile Ser Thr Lys Ala Val Gly Gln Asp Arg Arg Arg
 420 425 430

Asp Ile Thr Tyr Glu Tyr Lys Tyr Pro Glu Gly Ser Ser Glu Glu Arg
 435 440 445

Gln Val Met Asp His Ala Phe Leu Leu Ser Ser Glu Arg Glu His
 450 455 460

Arg Arg Pro Val Lys Glu Asn Phe Leu His Met Ser Val Gln Ser Asp
 465 470 475 480

Asp Val Leu Leu Gly Asn Ser Val Asn Phe Thr Val Ile Leu Lys Arg
 485 490 495

Lys Thr Ala Ala Leu Gln Asn Val Asn Ile Leu Gly Ser Phe Glu Leu
 500 505 510

Gln Leu Tyr Thr Gly Lys Lys Met Ala Lys Leu Cys Asp Leu Asn Lys
 515 520 525

Thr Ser Gln Ile Gln Gly Gln Val Ser Glu Val Thr Leu Thr Leu Asp
 530 535 540

Ser Lys Thr Tyr Ile Asn Ser Leu Ala Ile Leu Asp Asp Glu Pro Val
 545 550 555 560
 Ile Arg Gly Phe Ile Ile Ala Glu Ile Val Glu Ser Lys Glu Ile Met
 565 570 575

 Ala Ser Glu Val Phe Thr Ser Phe Gln Tyr Pro Glu Phe Ser Ile Glu
 580 585 590

 Leu Pro Asn Thr Gly Arg Ile Gly Gln Leu Leu Val Cys Asn Cys Ile
 595 600 605

 Phe Lys Asn Thr Leu Ala Ile Pro Leu Thr Asp Val Lys Phe Ser Leu
 610 615 620

 Glu Ser Leu Gly Ile Ser Ser Leu Gln Thr Ser Asp His Gly Thr Val
 625 630 635 640

 Gln Pro Gly Glu Thr Ile Gln Ser Gln Ile Lys Cys Thr Pro Ile Lys
 645 650 655

 Thr Gly Pro Lys Lys Phe Ile Val Lys Leu Ser Ser Lys Gln Val Lys
 660 665 670

 Glu Ile Asn Ala Gln Lys Ile Val Leu Ile Thr Lys
 675 680

 <210> 776
 <211> 679
 <212> PRT
 <213> Homo sapiens

 <400> 776
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 Asn Gln Asp Asn Ala Val Ser His His Thr Trp Glu Phe Gln Thr Ser
 20 25 30

 Ser Pro Val Phe Arg Arg Gly Gln Val Phe His Leu Arg Leu Val Leu
 35 40 45

 Asn Gln Pro Leu Gln Ser Tyr His Gln Leu Lys Leu Glu Phe Ser Thr
 50 55 60

 Gly Pro Asn Pro Ser Ile Ala Lys His Thr Leu Val Val Leu Asp Pro
 65 70 75 80

 Arg Thr Pro Ser Asp His Tyr Asn Trp Gln Ala Thr Leu Gln Asn Glu
 85 90 95

Ser Gly Lys Glu Val Thr Val Ala Val Thr Ser Ser Pro Asn Ala Ile
 100 105 110
 Leu Gly Lys Tyr Gln Leu Asn Val Lys Thr Gly Asn His Ile Leu Lys
 115 120 125
 Ser Glu Glu Asn Ile Leu Tyr Leu Leu Phe Asn Pro Trp Cys Lys Glu
 130 135 140
 Asp Met Val Phe Met Pro Asp Glu Asp Glu Arg Lys Glu Tyr Ile Leu
 145 150 155 160
 Asn Asp Thr Gly Cys His Tyr Val Gly Ala Ala Arg Ser Ile Lys Cys
 165 170 175
 Lys Pro Trp Asn Phe Gly Gln Phe Glu Lys Asn Val Leu Asp Cys Cys
 180 185 190
 Ile Ser Leu Leu Thr Glu Ser Ser Leu Lys Pro Thr Asp Arg Arg Asp
 195 200 205
 Pro Val Leu Val Cys Arg Ala Met Cys Ala Met Met Ser Phe Glu Lys
 210 215 220
 Gly Gln Gly Val Leu Ile Gly Asn Trp Thr Gly Asp Tyr Glu Gly Gly
 225 230 235 240
 Thr Ala Pro Tyr Lys Trp Thr Gly Ser Ala Pro Ile Leu Gln Gln Tyr
 245 250 255
 Tyr Asn Thr Lys Gln Ala Val Cys Phe Gly Gln Cys Trp Val Phe Ala
 260 265 270
 Gly Ile Leu Thr Thr Val Leu Arg Ala Leu Gly Ile Pro Ala Arg Ser
 275 280 285
 Val Thr Gly Phe Asp Ser Ala His Asp Thr Glu Arg Asn Leu Thr Val
 290 295 300
 Asp Thr Tyr Val Asn Glu Asn Gly Glu Lys Ile Thr Ser Met Thr His
 305 310 315 320
 Asp Ser Val Trp Asn Phe His Val Trp Thr Asp Ala Trp Met Lys Arg
 325 330 335
 Pro Tyr Asp Gly Trp Gln Ala Val Asp Ala Thr Pro Gln Glu Arg Ser
 340 345 350
 Gln Gly Val Phe Cys Cys Gly Pro Ser Pro Leu Thr Ala Ile Arg Lys
 355 360 365

Gly Asp Ile Phe Ile Val Tyr Asp Thr Arg Phe Val Phe Ser Glu Val
 370 375 380

Asn Gly Asp Arg Leu Ile Trp Leu Val Lys Met Val Asn Gly Gln Glu
 385 390 395 400

Glu Leu His Val Ile Ser Met Glu Thr Thr Ser Ile Gly Lys Asn Ile
 405 410 415

Ser Thr Lys Ala Val Gly Gln Asp Arg Arg Arg Asp Ile Thr Tyr Glu
 420 425 430

Tyr Lys Tyr Pro Glu Gly Ser Ser Glu Glu Arg Gln Val Met Asp His
 435 440 445

Ala Phe Leu Leu Leu Ser Ser Glu Arg Glu His Arg Gln Pro Val Lys
 450 455 460

Glu Asn Phe Leu His Met Ser Val Gln Ser Asp Asp Val Leu Leu Gly
 465 470 475 480

Asn Ser Val Asn Phe Thr Val Ile Leu Lys Arg Lys Thr Ala Ala Leu
 485 490 495

Gln Asn Val Asn Ile Leu Gly Ser Phe Glu Leu Gln Leu Tyr Thr Gly
 500 505 510

Lys Lys Met Ala Lys Leu Cys Asp Leu Asn Lys Thr Ser Gln Ile Gln
 515 520 525

Gly Gln Val Ser Glu Val Thr Leu Thr Leu Asp Ser Lys Thr Tyr Ile
 530 535 540

Asn Ser Leu Ala Ile Leu Asp Asp Glu Pro Val Ile Arg Gly Phe Ile
 545 550 555 560

Ile Ala Glu Ile Val Glu Ser Lys Glu Ile Met Ala Ser Glu Val Phe
 565 570 575

Thr Ser Asn Gln Tyr Pro Glu Phe Ser Ile Glu Leu Pro Asn Thr Gly
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Arg Ile Gly Gln Leu Leu Val Cys Asn Cys Ile Phe Lys Asn Thr Leu
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Ala Ile Pro Leu Thr Asp Val Lys Phe Ser Leu Glu Ser Leu Gly Ile
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Ile Gln Ser Gln Ile Lys Cys Thr Pro Ile Lys Thr Gly Pro Lys Lys
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<211> 1095

<212> PRT

<213> Homo sapiens

<400> 778

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Thr Lys Asp Ser Lys Ala Thr Glu Asn Val Cys Lys Cys Gly Tyr Ala			
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Gln Ser Gln His Met Glu Gly Thr Gln Ile Asn Gln Ser Glu Lys Trp			
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Asn Tyr Lys Lys His Thr Lys Glu Phe Pro Thr Asp Ala Phe Gly Asp			
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Ile Gln Phe Glu Thr Leu Gly Lys Lys Gly Lys Tyr Ile Arg Leu Ser			
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Cys Asp Thr Asp Ala Glu Ile Leu Tyr Glu Leu Leu Thr Gln His Trp			
115	120	125	

His Leu Lys Thr Pro Asn Leu Val Ile Ser Val Thr Gly Gly Ala Lys			
130	135	140	

Asn Phe Ala Leu Lys Pro Arg Met Arg Lys Ile Phe Ser Arg Leu Ile			
145	150	155	160

Tyr Ile Ala Gln Ser Lys Gly Ala Trp Ile Leu Thr Gly Gly Thr His			
165	170	175	

Tyr Gly Leu Thr Lys Tyr Ile Gly Glu Val Val Arg Asp Asn Thr Ile
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 Ser Arg Ser Ser Glu Glu Asn Ile Val Ala Ile Gly Ile Ala Ala Trp
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 Gly Met Val Ser Asn Arg Asp Thr Leu Ile Arg Asn Cys Asp Ala Glu
 210 215 220
 Gly Tyr Phe Leu Ala Gln Tyr Leu Met Asp Asp Phe Thr Arg Asp Pro
 225 230 235 240
 Leu Tyr Ile Leu Asp Asn Asn His Thr His Leu Leu Leu Val Asp Asn
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 Gly Cys His Gly His Pro Thr Val Glu Ala Lys Leu Arg Asn Gln Leu
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 Glu Lys His Ile Ser Glu Arg Thr Ile Gln Asp Ser Asn Tyr Gly Gly
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 305 310 315 320
 Glu Gly Ser Gly Arg Ile Ala Asp Val Ile Ala Ser Leu Val Glu Val
 325 330 335
 Glu Asp Ala Pro Thr Ser Ser Ala Val Lys Glu Lys Leu Val Arg Phe
 340 345 350
 Leu Pro Arg Thr Val Ser Arg Leu Ser Glu Glu Glu Thr Glu Ser Trp
 355 360 365
 Ile Lys Trp Leu Lys Glu Ile Leu Glu Cys Ser His Leu Leu Thr Val
 370 375 380
 Ile Lys Met Glu Glu Ala Gly Asp Glu Ile Val Ser Asn Ala Ile Ser
 385 390 395 400
 Tyr Ala Leu Tyr Lys Ala Phe Ser Thr Ser Glu Gln Asp Lys Asp Asn
 405 410 415
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 420 425 430
 Ala Asn Asp Glu Ile Phe Thr Asn Asp Arg Arg Trp Glu Ser Ala Asp
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Leu Gln Glu Val Met Phe Thr Ala Leu Ile Lys Asp Arg Pro Lys Phe
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Val Arg Leu Phe Leu Glu Asn Gly Leu Asn Leu Arg Lys Phe Leu Thr
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His Asp Val Leu Thr Glu Leu Phe Ser Asn His Phe Ser Thr Leu Val
 485 490 495

Tyr Arg Asn Leu Gln Ile Ala Lys Asn Ser Tyr Asn Asp Ala Leu Leu
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Thr Phe Val Trp Lys Leu Val Ala Asn Phe Arg Arg Gly Phe Arg Lys
 515 520 525

Glu Asp Arg Asn Gly Arg Asp Glu Met Asp Ile Glu Leu His Asp Val
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Ser Pro Ile Thr Arg His Pro Leu Gln Ala Leu Phe Ile Trp Ala Ile
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Leu Gln Asn Lys Lys Glu Leu Ser Lys Val Ile Trp Glu Gln Thr Arg
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Gly Cys Thr Leu Ala Ala Leu Gly Ala Ser Lys Leu Leu Lys Thr Leu
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Ala Lys Val Lys Asn Asp Ile Asn Ala Ala Gly Glu Ser Glu Glu Leu
 595 600 605

Ala Asn Glu Tyr Glu Thr Arg Ala Val Glu Leu Phe Thr Glu Cys Tyr
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Ser Ser Asp Glu Asp Leu Ala Glu Gln Leu Leu Val Tyr Ser Cys Glu
 625 630 635 640

Ala Trp Gly Gly Ser Asn Cys Leu Glu Leu Ala Val Glu Ala Thr Asp
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Gln His Phe Thr Ala Gln Pro Gly Val Gln Asn Phe Leu Ser Lys Gln
 660 665 670

Trp Tyr Gly Glu Ile Ser Arg Asp Thr Lys Asn Trp Lys Ile Ile Leu
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Cys Leu Phe Ile Ile Pro Leu Val Gly Cys Gly Phe Val Ser Phe Arg
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Lys Lys Pro Val Asp Lys His Lys Lys Leu Leu Trp Tyr Tyr Val Ala
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Ile Ala Phe Leu Leu Leu Phe Ala Tyr Val Leu Leu Met Asp Phe His
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Ile Ala Gly Ile Val Phe Arg Leu His Ser Ser Asn Lys Ser Ser Leu
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Tyr Ser Gly Arg Val Ile Phe Cys Leu Asp Tyr Ile Ile Phe Thr Leu
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Arg Leu Ile His Ile Phe Thr Val Ser Arg Asn Leu Gly Pro Lys Ile
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Ile Met Leu Gln Arg Met Leu Ile Asp Val Phe Phe Leu Phe Leu
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Phe Ala Val Trp Met Val Ala Phe Gly Val Ala Arg Gln Gly Ile Leu
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Arg Gln Asn Glu Gln Arg Trp Arg Trp Ile Phe Arg Ser Val Ile Tyr
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Glu Pro Tyr Leu Ala Met Phe Gly Gln Val Pro Ser Asp Val Asp Gly
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Thr Thr Tyr Asp Phe Ala His Cys Thr Phe Thr Gly Asn Glu Ser Lys
 915 920 925

Pro Leu Cys Val Glu Leu Asp Glu His Asn Leu Pro Arg Phe Pro Glu
 930 935 940

Trp Ile Thr Ile Pro Leu Val Cys Ile Tyr Met Leu Ser Thr Asn Ile
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Leu Leu Val Asn Leu Leu Val Ala Met Phe Gly Tyr Thr Val Gly Thr
 965 970 975

Val Gln Glu Asn Asn Asp Gln Val Trp Lys Phe Gln Arg Tyr Phe Leu
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Val Gln Glu Tyr Cys Ser Arg Leu Asn Ile Pro Phe Pro Phe Ile Val
 995 1000 1005

 Phe Ala Tyr Phe Tyr Met Val Val Lys Lys Cys Phe Lys Cys Cys Cys
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 Lys Glu Lys Asn Met Glu Ser Ser Val Cys Cys Phe Lys Asn Glu Asp
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 Asn Glu Thr Leu Ala Trp Glu Gly Val Met Lys Glu Asn Tyr Leu Val
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 Lys Ile Asn Thr Lys Ala Asn Asp Thr Ser Glu Glu Met Arg His Arg
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<210> 780
 <211> 1095
 <212> PRT
 <213> Homo sapiens

<220>
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 <223> Xaa = Any Amino Acid

<400> 780

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Asn	Tyr	Lys	Lys	His	Thr	Lys	Glu	Phe	Pro	Thr	Asp	Ala	Phe	Gly	Asp
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His	Leu	Lys	Thr	Pro	Asn	Leu	Val	Ile	Ser	Val	Thr	Gly	Gly	Ala	Lys
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Tyr	Ile	Ala	Gln	Ser	Lys	Gly	Ala	Trp	Ile	Leu	Thr	Gly	Gly	Thr	His
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Leu	Tyr	Ile	Leu	Asp	Asn	Asn	His	Thr	His	Leu	Leu	Leu	Val	Asp	Asn
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Gly	Cys	His	Gly	His	Pro	Thr	Val	Glu	Ala	Lys	Leu	Arg	Asn	Gln	Leu
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Glu	Gly	Ser	Gly	Gln	Ile	Ala	Asp	Val	Ile	Ala	Ser	Leu	Val	Glu	Val
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Glu	Asp	Ala	Leu	Thr	Ser	Ser	Ala	Val	Lys	Glu	Lys	Leu	Val	Arg	Phe
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Leu	Pro	Arg	Thr	Val	Ser	Arg	Leu	Pro	Glu	Glu	Glu	Thr	Glu	Ser	Trp
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Ile	Lys	Trp	Leu	Lys	Glu	Ile	Leu	Glu	Cys	Ser	His	Leu	Leu	Thr	Val
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Ile	Lys	Met	Glu	Glu	Ala	Gly	Asp	Glu	Ile	Val	Ser	Asn	Ala	Ile	Ser
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Tyr	Ala	Leu	Tyr	Lys	Ala	Phe	Ser	Thr	Ser	Glu	Gln	Asp	Lys	Asp	Asn
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Trp	Asn	Gly	Gln	Leu	Lys	Leu	Leu	Glu	Trp	Asn	Gln	Leu	Asp	Leu	
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Ala	Asn	Asp	Glu	Ile	Phe	Thr	Asn	Asp	Arg	Arg	Trp	Glu	Ser	Ala	Asp
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Leu	Gln	Glu	Val	Met	Phe	Thr	Ala	Leu	Ile	Lys	Asp	Arg	Pro	Lys	Phe
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His	Asp	Val	Leu	Thr	Glu	Leu	Phe	Ser	Asn	His	Phe	Ser	Thr	Leu	Val
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Tyr	Arg	Asn	Leu	Gln	Ile	Ala	Lys	Asn	Ser	Tyr	Asn	Asp	Ala	Leu	Leu
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Thr	Phe	Val	Trp	Lys	Leu	Val	Ala	Asn	Phe	Arg	Arg	Gly	Phe	Arg	Lys
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Glu	Asp	Arg	Asn	Gly	Arg	Asp	Glu	Met	Asp	Ile	Glu	Leu	His	Asp	Val
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Pro Leu Cys Val Glu Leu Asp Glu His Asn Leu Pro Arg Phe Pro Glu
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Trp Ile Thr Ile Pro Leu Val Cys Ile Tyr Met Leu Ser Thr Asn Ile
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Leu Leu Val Asn Leu Leu Val Ala Met Phe Gly Tyr Thr Val Gly Thr
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